Sepsis

Pearls & Pitfalls in Infectious Diseases

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Present illness

- Previous status : Could do ADL functional class I
- **CC: fever with chill for 1 day PTA**
- Underlying: CA colon (adenocarcinoma) present with clinical gut obstruction 6 wks before this admission (24/1/2559)

9/12/58
Clinical gut obstruction
Colonoscope: mass at sigmoid colon 5 x 4 cm bx: adeno CA

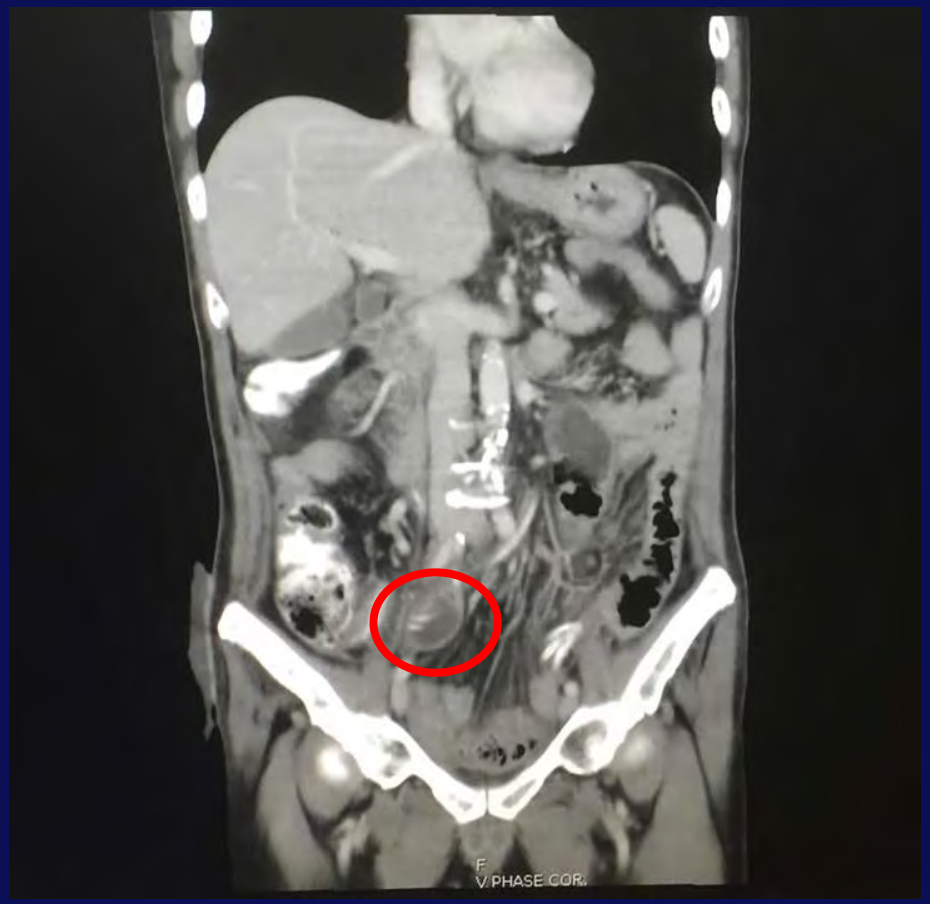
Dx: CA sigmoid colon invade bladder with obstruction

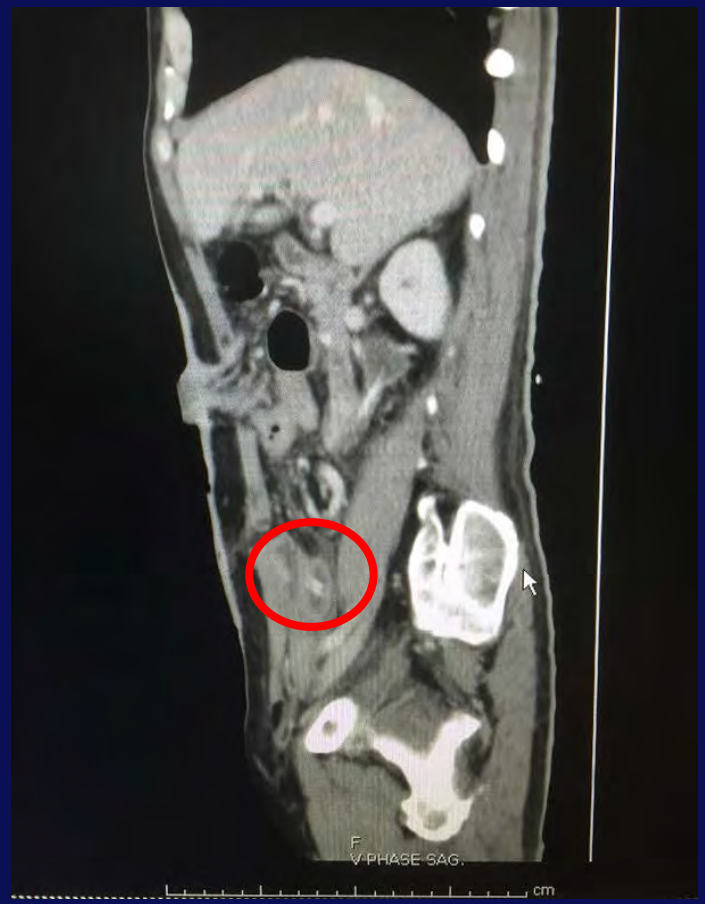
12/12/58
Flexible cystoscopy with loop transverse colostomy

19/12/58
Pelvic exenteration with ileal conduit

2/1/59 post op 2 wks
Fever with chill
CT abdomen (4/01/59)
H/C NG,
Rx meropenem x 10 days

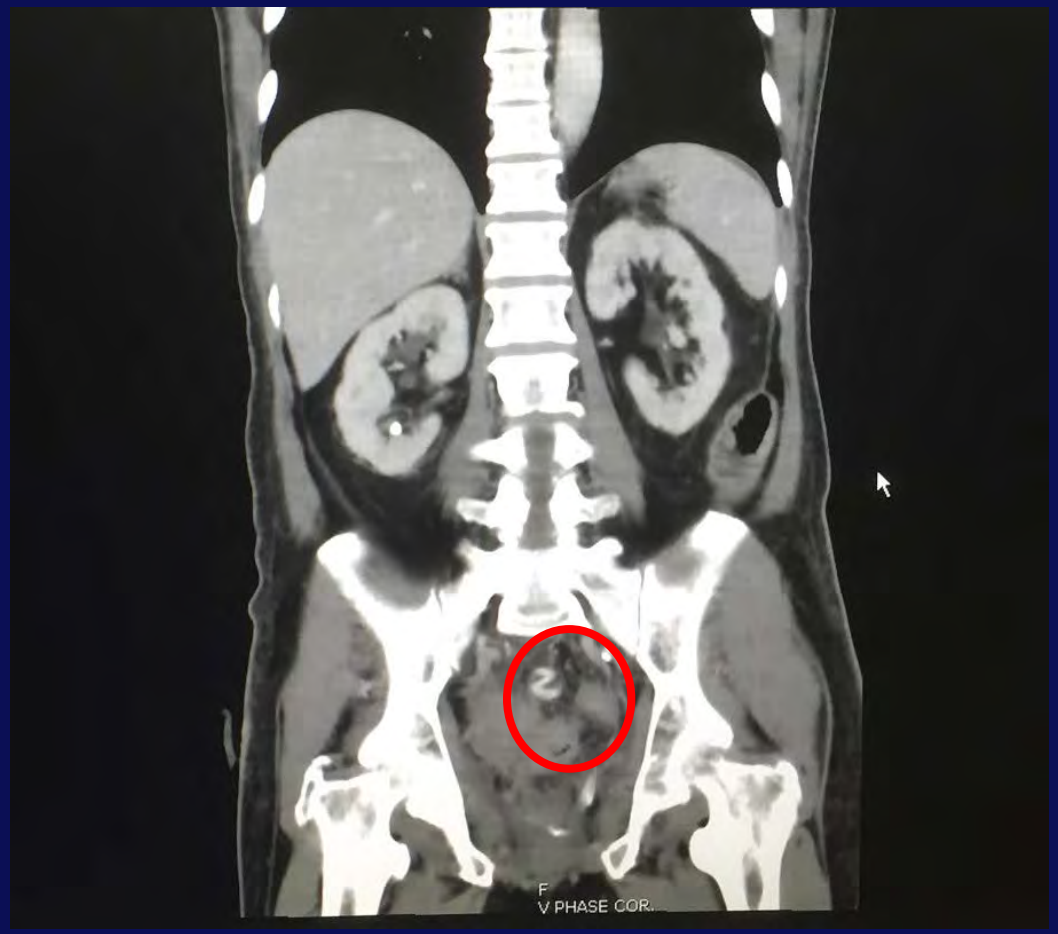
4/1/2559

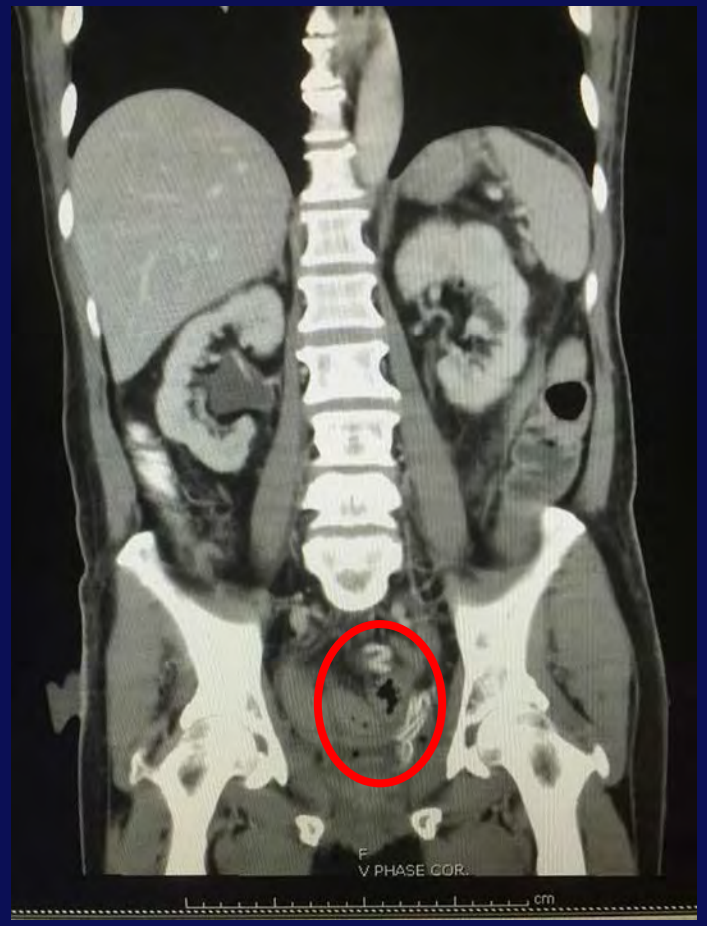




There is a rim enhancing fluid collection in pelvic cavity measuring about 1.2x8.7 cm

4/1/2559





There is another 4.3 x 4.3 cm rim-enhancing fluid collection with internal air bubbles in pelvic cavity

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Pelvic exenteration with ileal conduit

2/1/59 post op 2 wks
Fever with chill
CT abdomen (4/01/59)
H/C NG,
Rx meropenem x 10 days

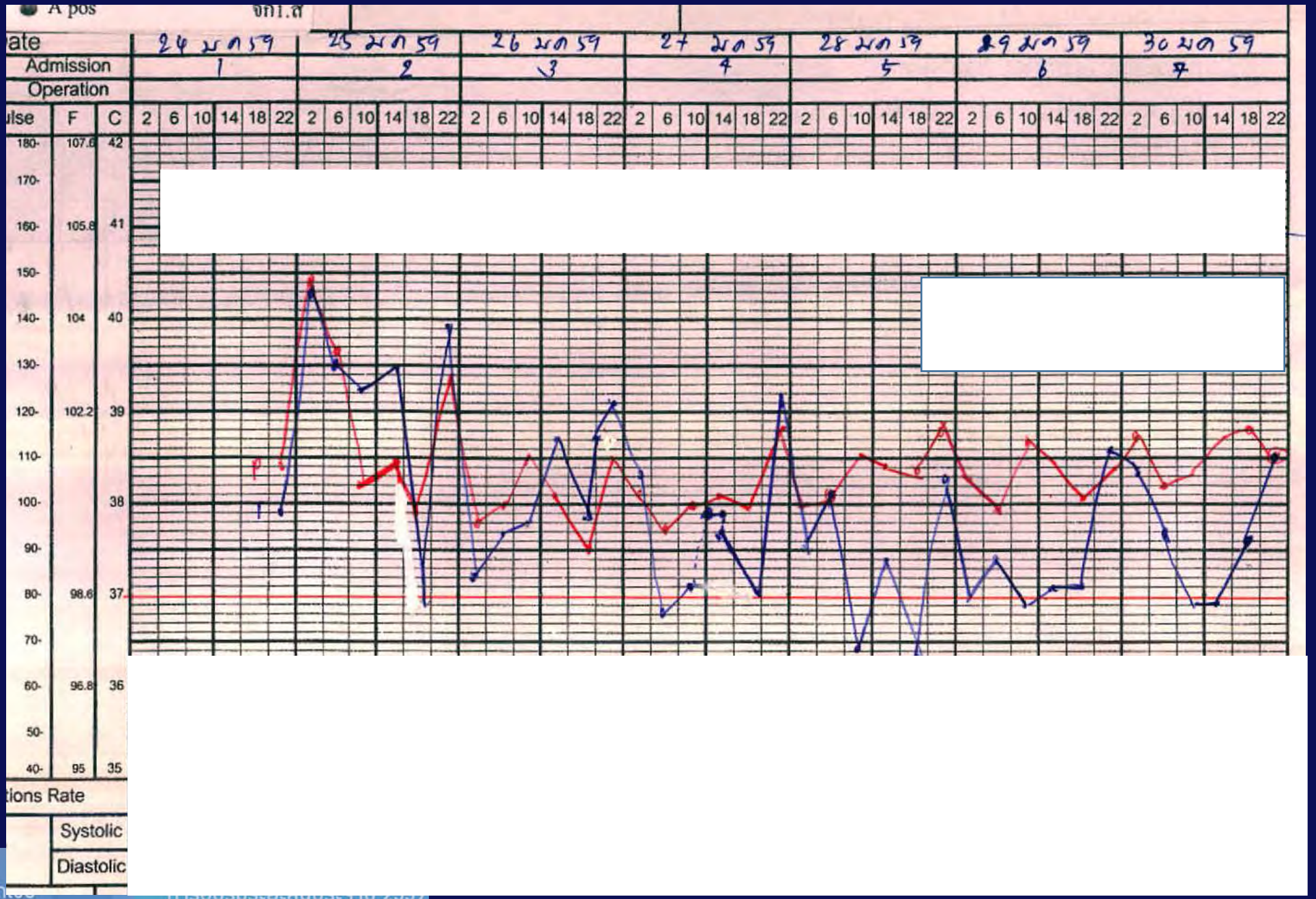
12/1/59
D/C
Off drain

Developed fever with chill 1 day PTA (2 weeks after previous admission)

Physical examination

- A middle aged Thai male patient, alert
- **GA: drowsiness**
- **BT 41C, RR 24/min, PR 150 bpm regular, BP 90/60 mmHg**
- Skin: normal skin turgor
- HEENT: not pale conjunctiva, anicteric sclera
- Lung: tachypnea, trachea in midline, equal, no adventitious sound
- Abdomen: colostomy, active bowel sound

Load NSS fluid 500 cc at ER → BP 110/70



SEPSIS BEDSIDE CRITERIA

JAMA. 2016;315(8):801-810.

NAME AGE WARD HOSPITAL No.

	DATE	24/1/59	25/1/59	26/1	27/1/59	30/1/59	31/1	1/2/59	2/2/59	3/2/59
AUTOMATED CBC	RBC									
	HGB	8	8	7.8	11	9	8.7	8.7	4.01	10.6
	HCT	25	25	23	33	28	26.5	26.1	38.4	32.5
	MCV							[illegible]	[illegible]	81.9
	MCH									
	MCHC									
	RDW									
	WBC	21,160	18,680	15730	13,380	9,940	1950	11,370	11,220	11,370
	% LYM N	94	95	93	90	78	75	83.7	74.0	79
	MO(MID) L	2	1	2.6	4	10	12	8.4	11.2	12.0
	GR									
	# LYM									
	MO(MID)									
	GR									
	PLATELETS	361,000	339,000	242000	246,000	385,000	272000	386,000	377,000	387,000
	PT/INR	15.5/1.29								
	PTT	30.9								

Creatinine baseline 1.02

AGE WARD HOSPITAL No.

DATE	24/1/59	25/1/59	26/1	26/1/59	27/1/59	28/1/59	29/1/59	31/1	1/2/59
GLUCOSE									
BUN	47	46	41	40	38	26	23	16	12
CREATININE	1.72	1.97	1.61	1.51	1.43	1.26	1.17	1.19	1.3
URIC ACID	Creatinine baseline 1.02								
BILIRUBIN, TOTAL	1.15	1.14							
BILIRUBIN, DIRECT	0.7	0.78							
ALK PHOSPHATASE	129	126							
SGOT	24	22							
SGPT	30	29							
LDH									
CPK									
PROTHROMBIN TIME									
ALBUMIN	3.2	3.1		2.6				2.3	
GLOBULIN									
CALCIUM	9			8		7.3	7.1	7.0	8.4
PHOSPHATE	2.3			1.9		1.7	1.5	1.2	2.3

Na 135, K 4.5, CL 100, HCO3 14, Lactate 2

SEPSIS CLINICAL CRITERIA

INFECTION

\+

CHANGE IN:

SEPSIS-RELATED
ORGAN
FAILURE
ASSESSMENT

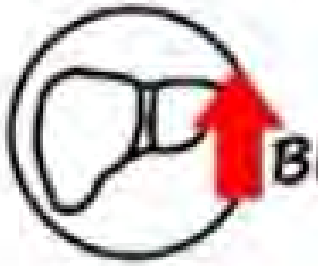
≥2

PaO_2 / FiO_2

HYPOTENSION OR VASOPRESSORS

PLATELETS

GLASGOW COMA SCALE



BILIRUBIN

CREATININE, OLIGURIA

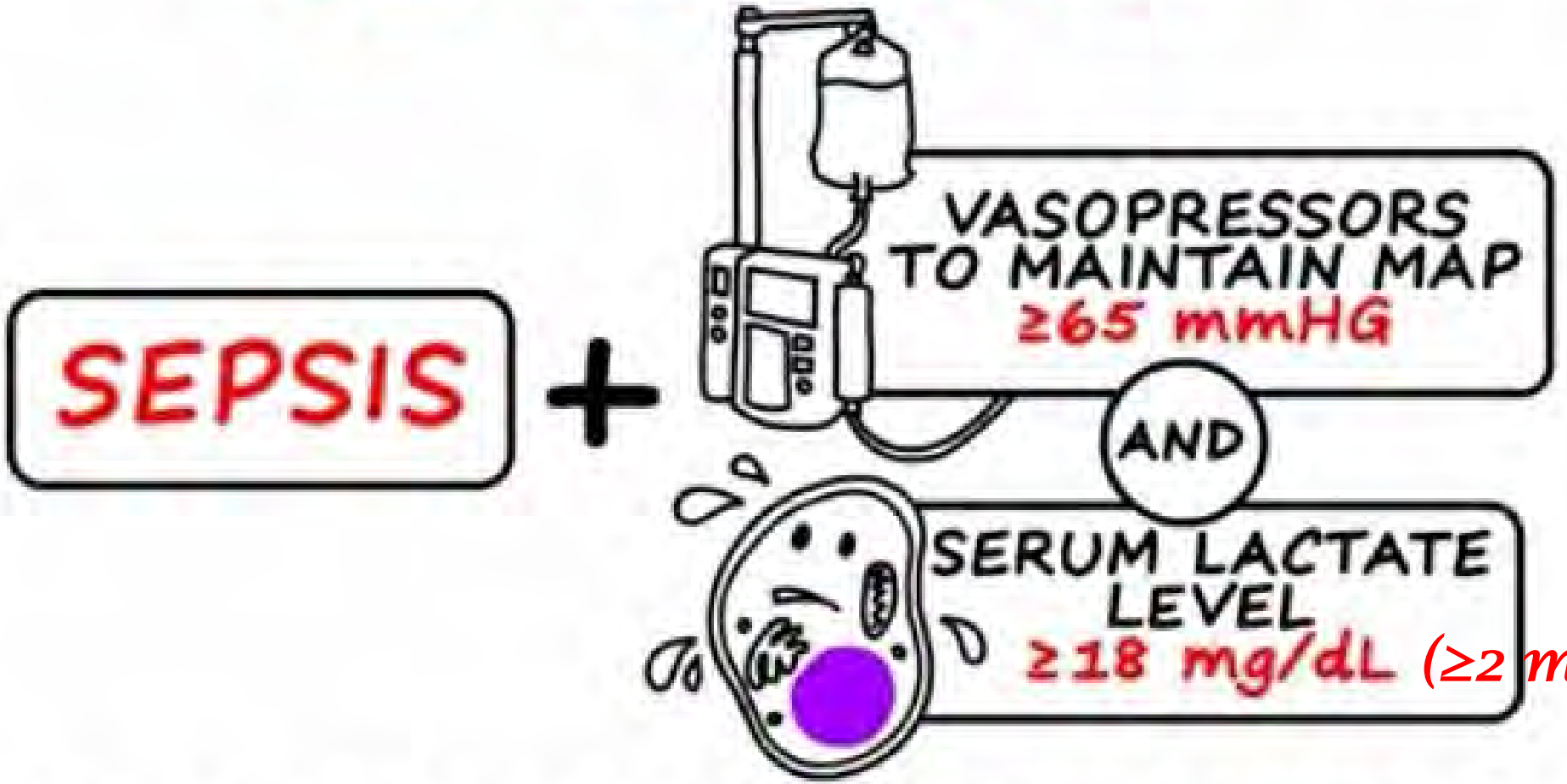
JAMA. 2016;315(8):801-810.

Sequential [Sepsis-Related] Organ Failure Assessment Score

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

JAMA. 2016;315(8):801-810.

SEPTIC SHOCK



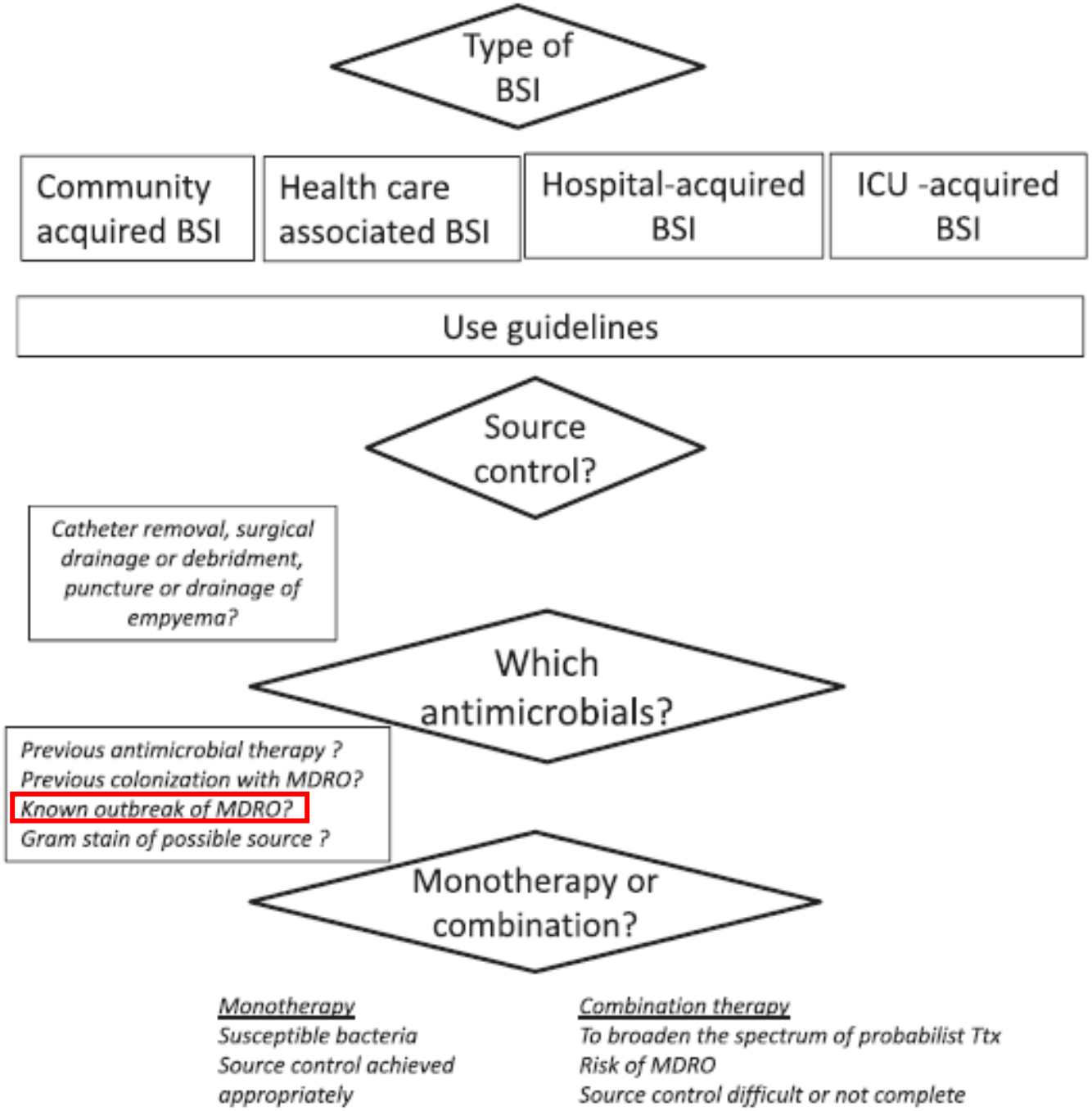
IN THE ABSENCE OF HYPOVOLEMIA

JAMA. 2016;315(8):801-810.

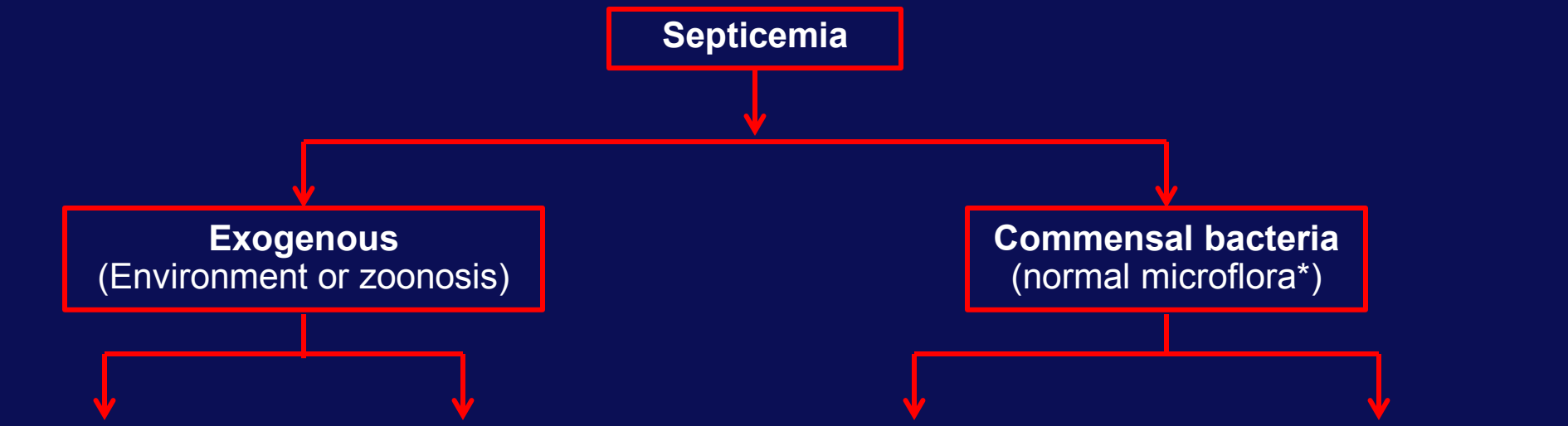
What is the best empirical antibiotic (s)?

Have a guess! What's organism??

1. *Acinetobacter baumanni*
2. *Pseudomonas aeruginosa*
3. *Stenotrophomonas maltophilia*
4. *Klebsiella pneumoniae*



BMC Infectious Diseases 2014, 14:489



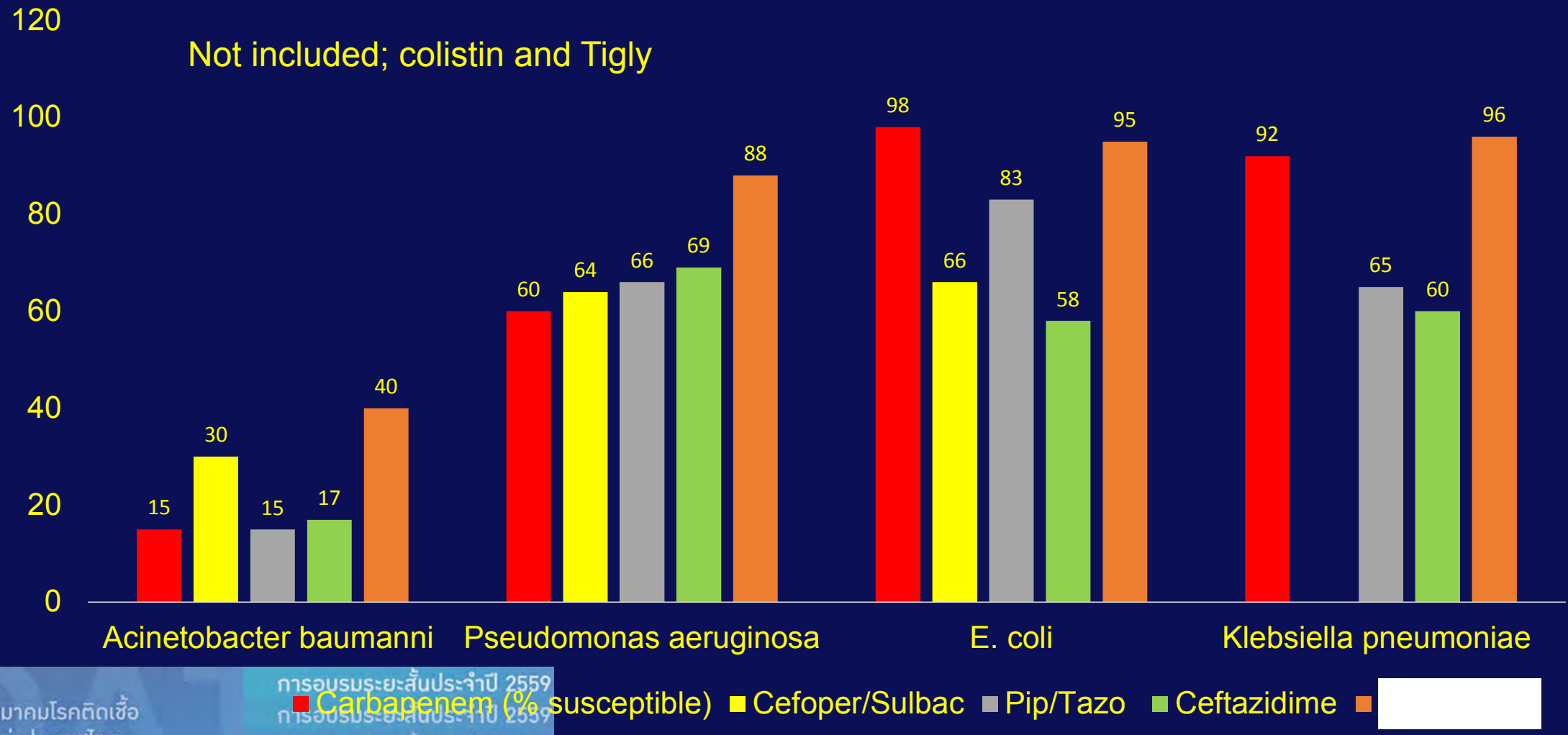
* Microflora in special population: ICU patient, prolonged board spectrum antibiotic, neutropenia: Multi-drug resistance organism, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Candida* spp.

H/C: *Klebsiella pneumoniae x II* (8.5, 9 hr.)

Which is the best appropriate antibiotic?

1. Meropenem
2. Piperacillin/Tazobactam
3. Trimethoprim-sulfamethoxazole
4. Colistin
5. Fosfomycin
6. Colistin + Meropenem

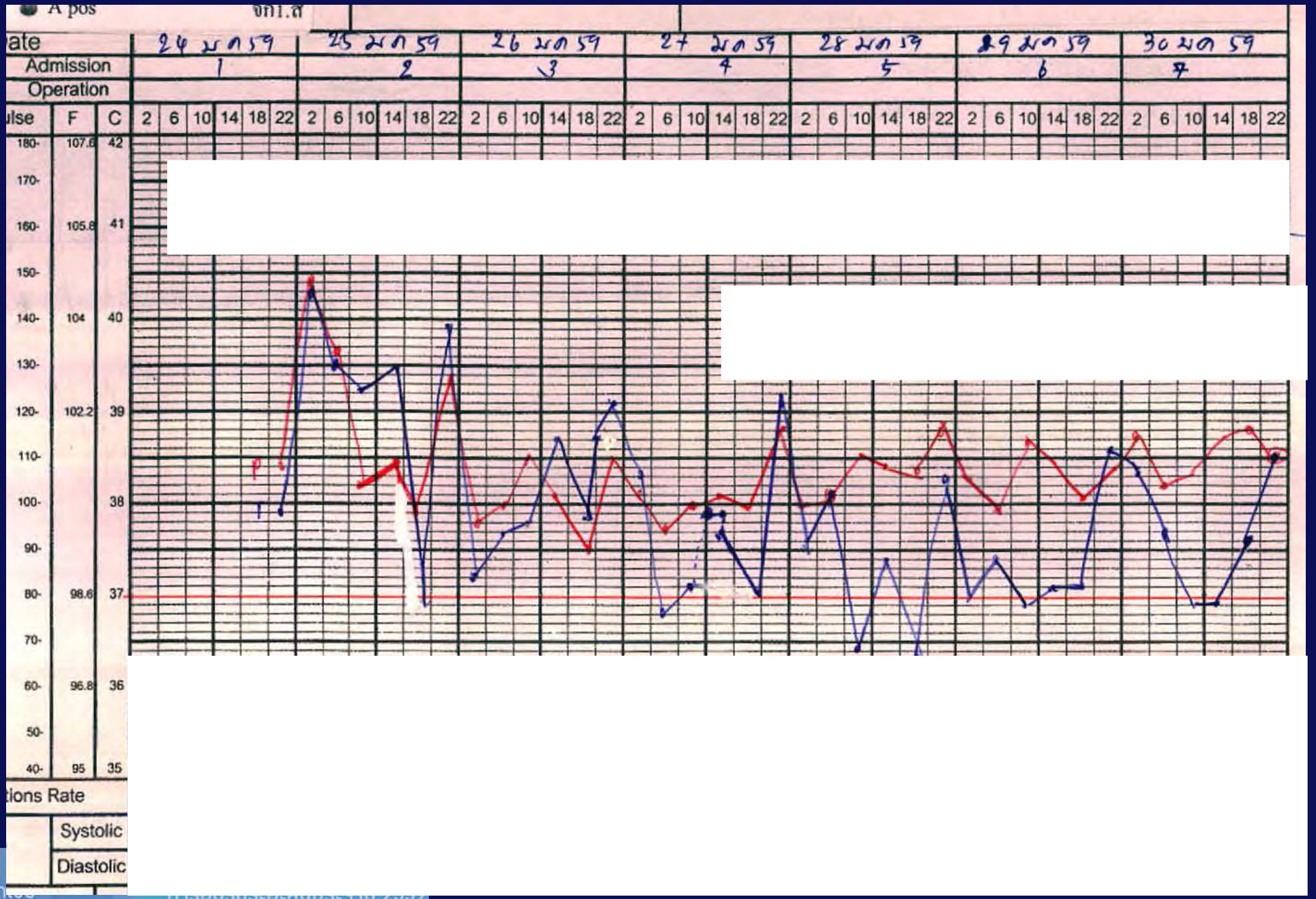
Percentage of susceptible bacteria department of microbiology Faculty of Medicine Chulalongkorn University 2014



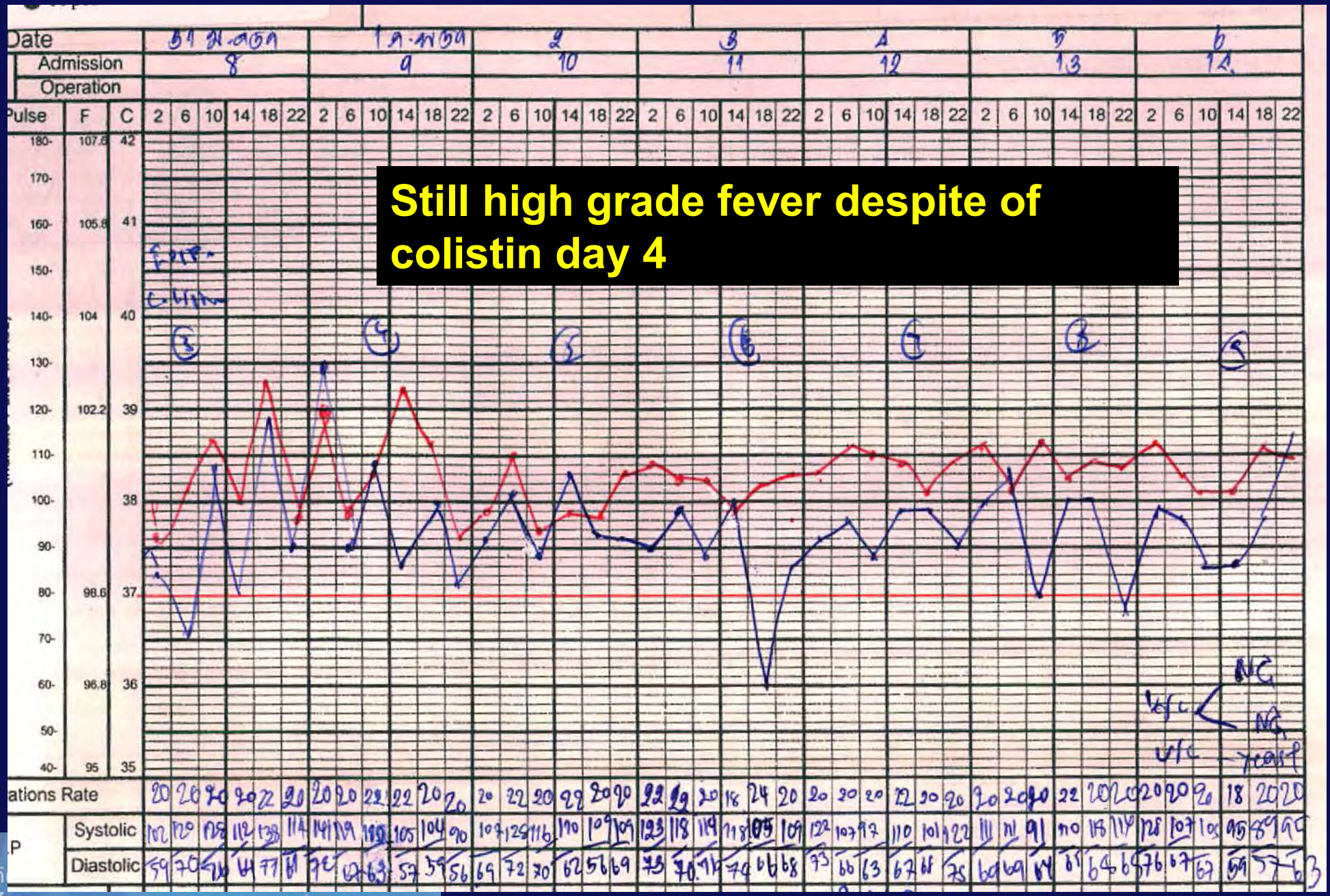
Accreditation No. 4112/55 Specimen :Blood วันที่ส่งตรวจ : 24/01/2559 22:44

รายการตรวจ [ชำระเงินแล้ว]/เชื้อ	จำนวนเชื้อ/ผลการทดสอบ	ยา	S/I/R	MIC	Unit
# Blood culture aerobic					
1. *Klebsiella pneumoniae*	-	Ampicillin	R		
		Cefazolin	R		
		Tetracycline	I		
		Amoxicillin/Clavulanic	R		
		Amikacin	R		
		Piperacillin/tazobactam	R		
		Cefotaxime	R		
		Ceftriaxone	R		
		Ceftazidime	R		
		Imipenem	R		
		Meropenem	R		
		Cefepime	R		
		Trimethoprim-sulfamethoxazole	S		
		Levofloxacin	R		
		Cefoxitin	R		
		Doripenem	R		

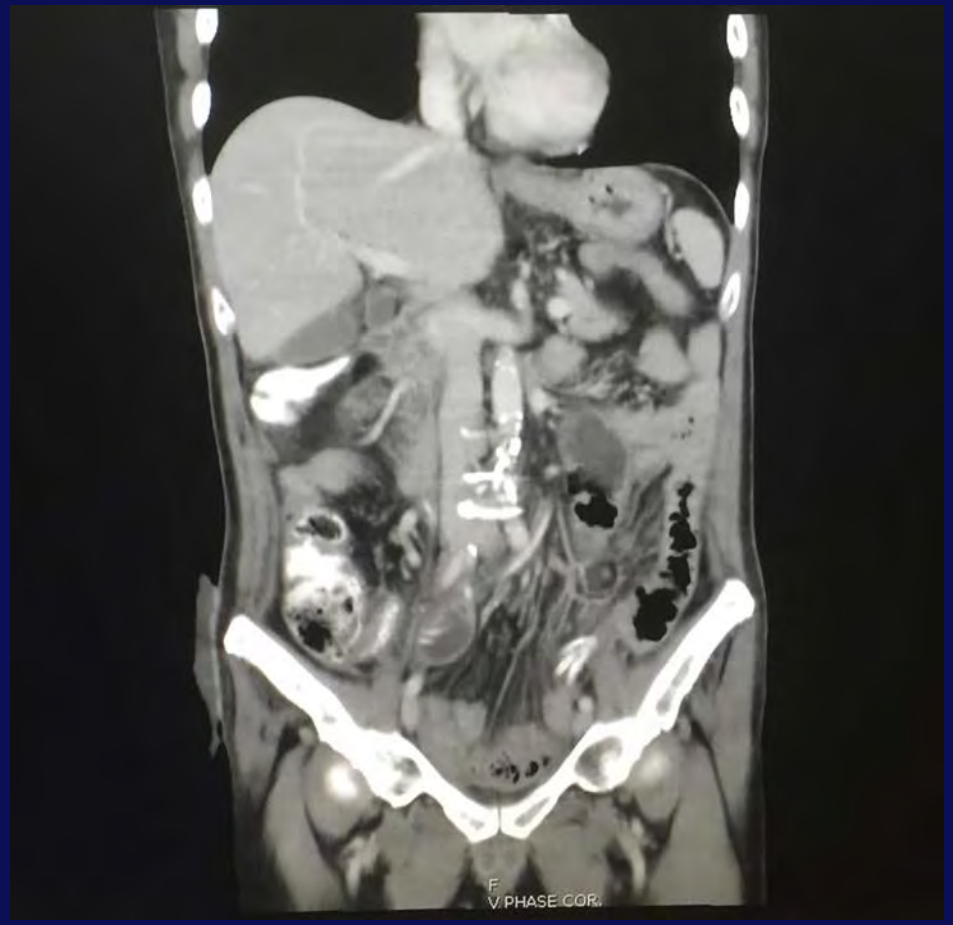
Positive at 10.3 hours.



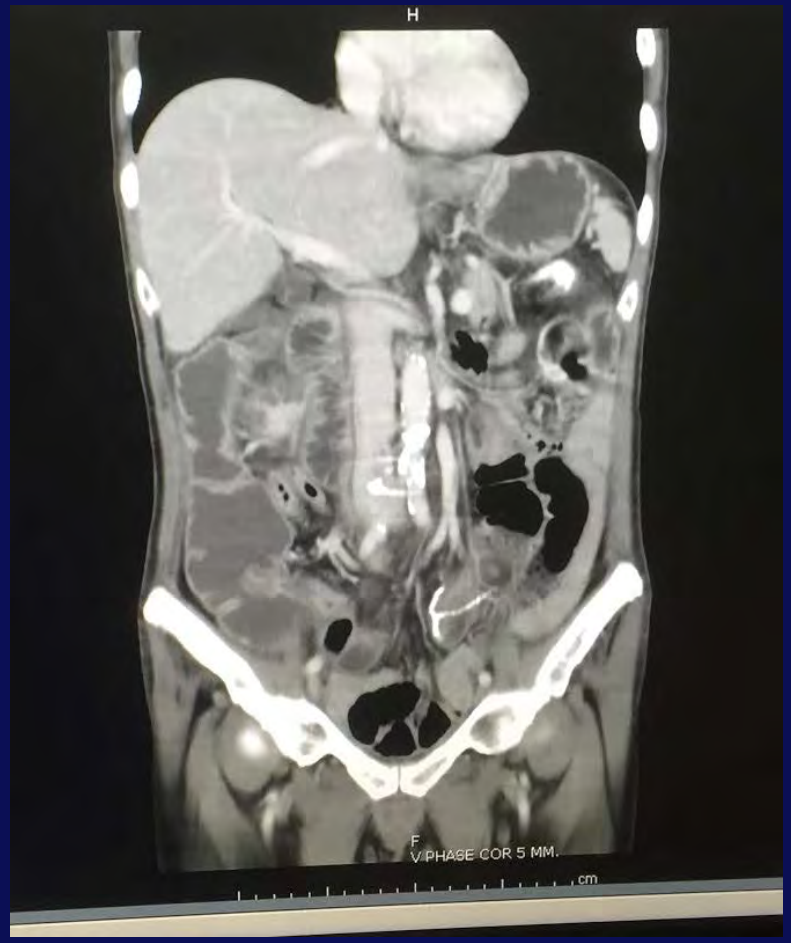
Doripenem	R	> 32	µg/mL
Fosfomycin	R	>1024	µg/mL
Imipenem	R	8	µg/mL
Meropenem	R	16	µg/mL
Colistin	-	2	µg/mL
Trimethoprim-sulfamethoxazole	S	0.125	µg/mL



4/1/2559

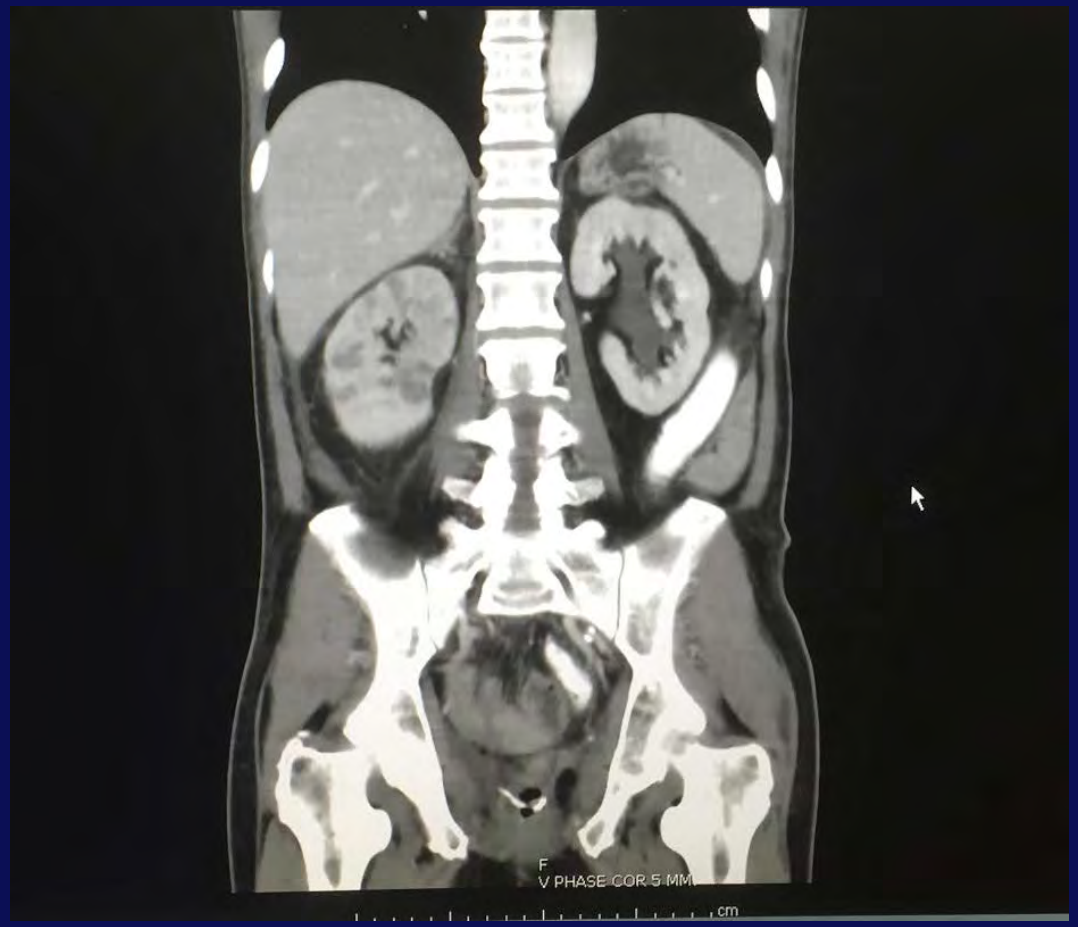


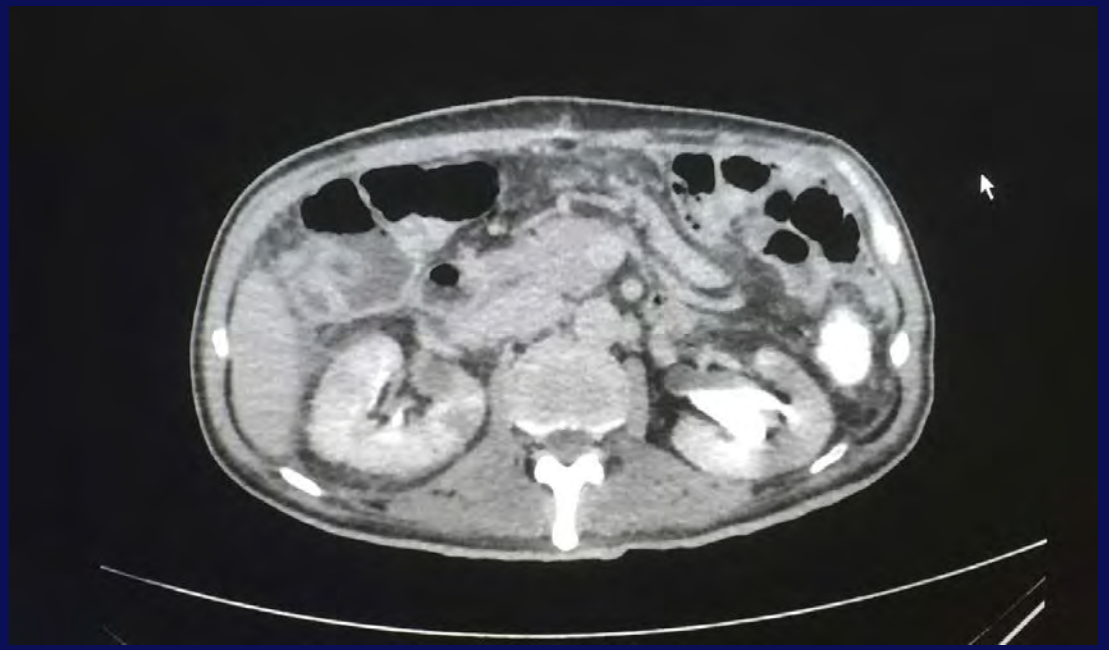
30/1/2559



Post removed drainage tube in pelvic cavity with resolution of 2 rim enhancing intraabdominal fluid collection as well as resolution of circumferential bowel wall thickening

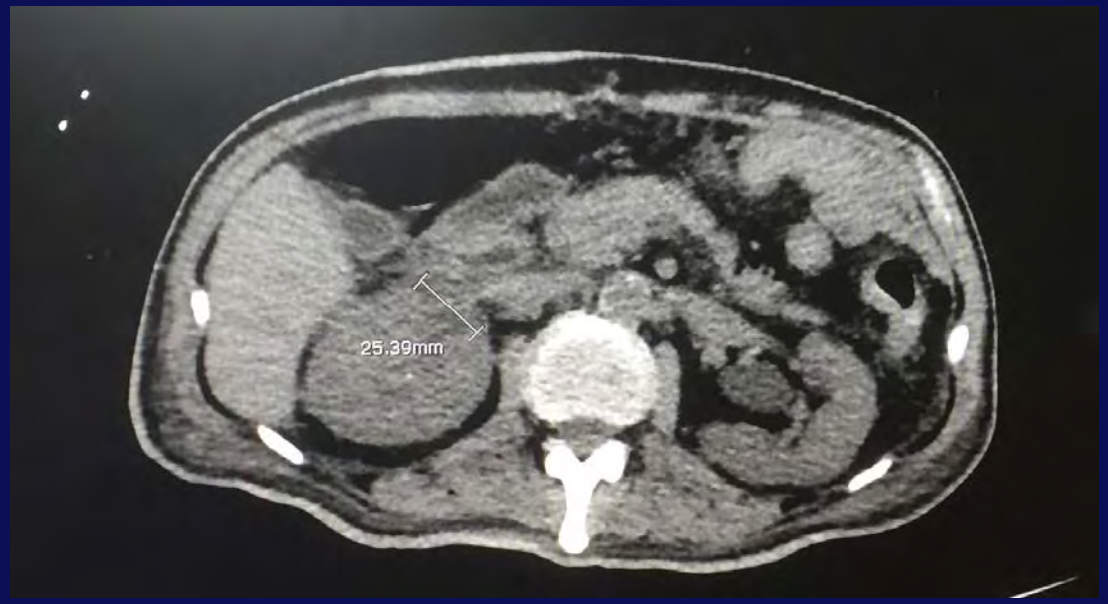
30/1/2559

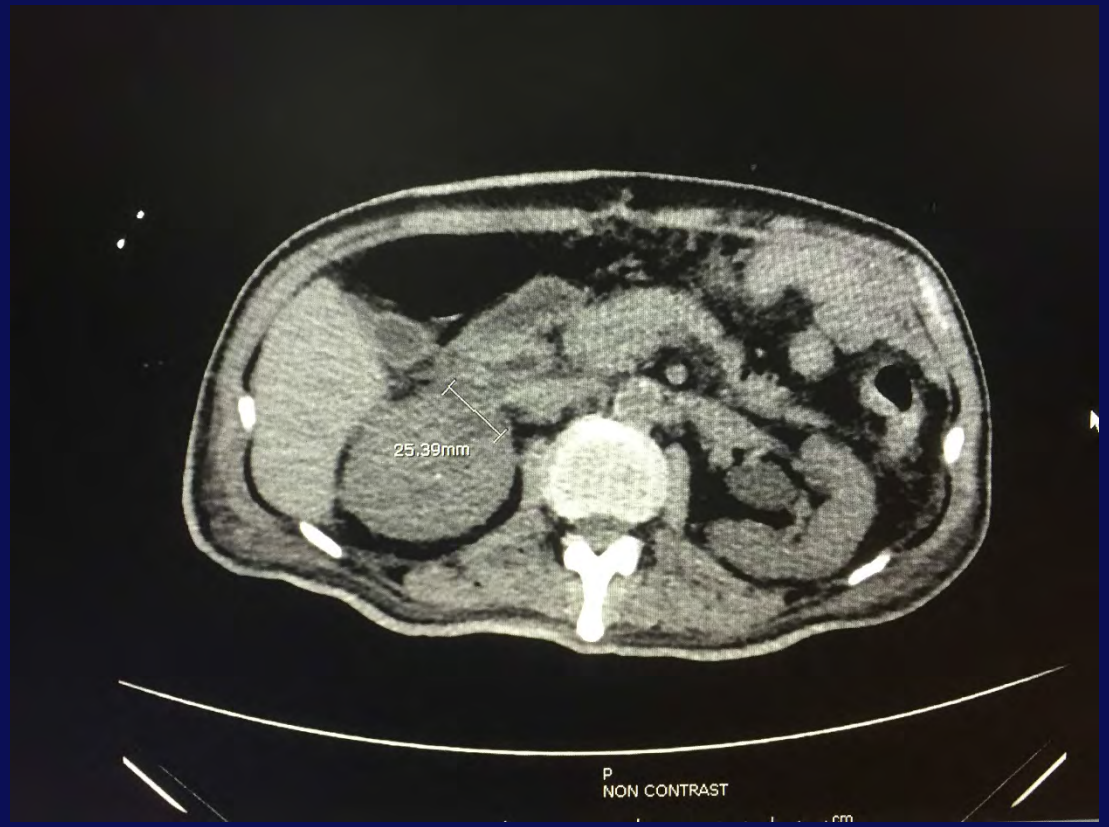




Interval developed ill defined hypodense lesions scatter in both renal parenchyma, more prominent in right side, probable lobar nephronia and/or early abscess formation

4/2/2559





Several ill defined hypodense lesions scattered in the right kidney, measured up to 2.5 cm with perinephric fat stranding and thickening of renal fascia likely abscess formation

7/2/2559

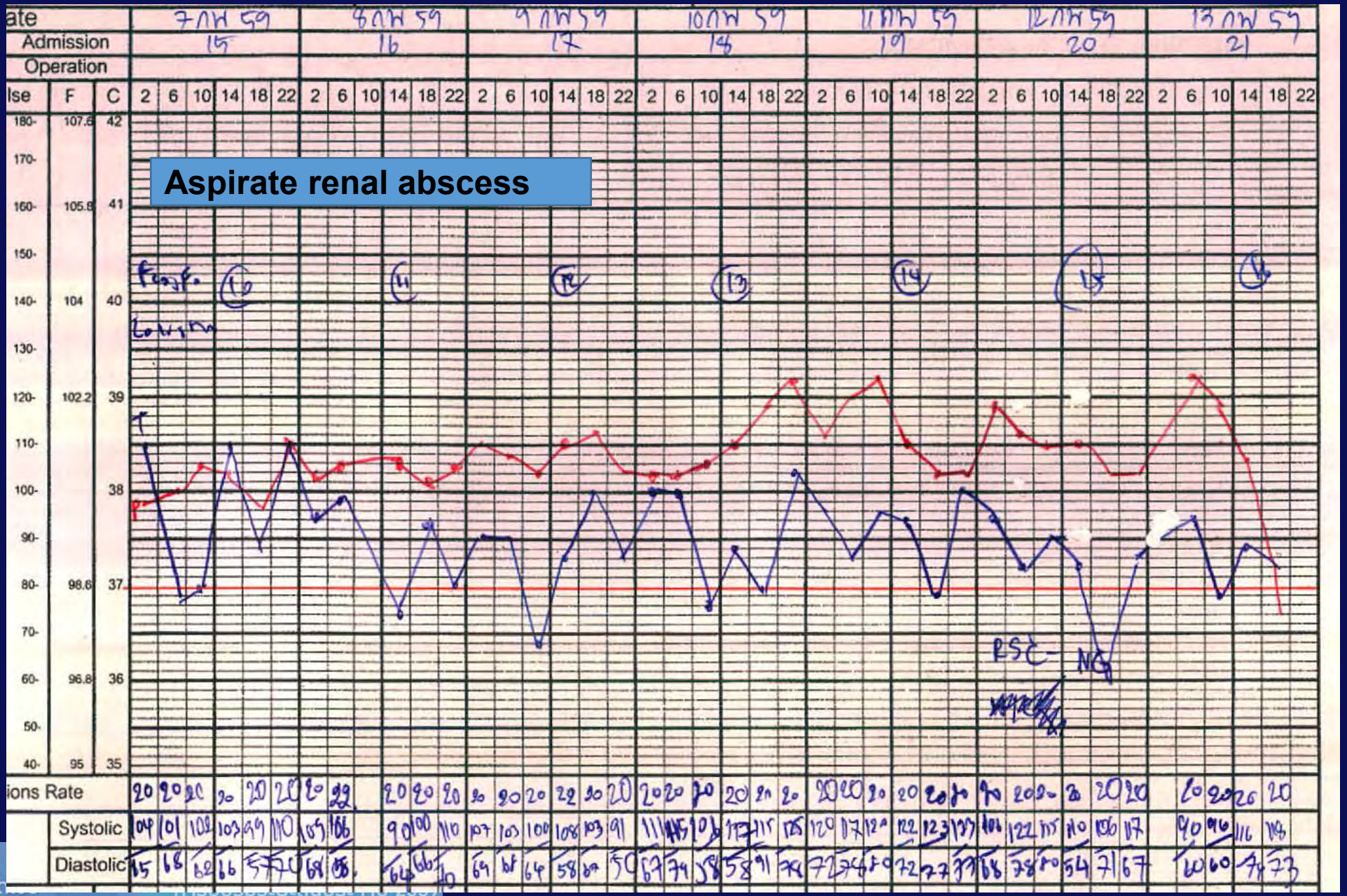
Interventionist
simple aspiration

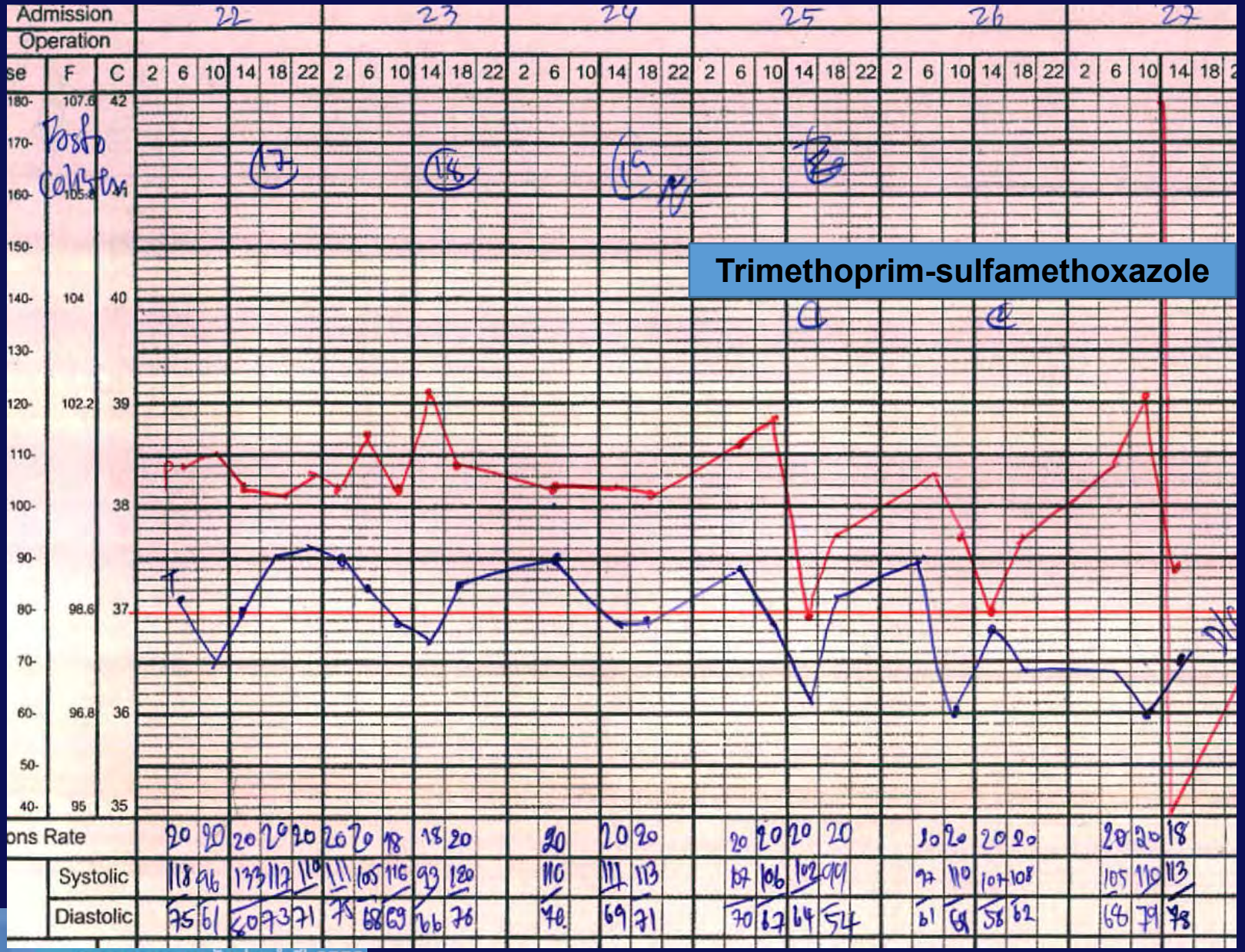
Turbid fluid 8 cc

รายการตรวจ [ชำระเงินแล้ว]/เชื้อ	จำนวนเชื้อ/ผลการทดสอบ	ยา	S/I/R	MIC	Unit
# Blood culture aerobic					
1. ***Klebsiella pneumoniae***	-	Ampicillin	R		
		Cefazolin	R		
		Tetracycline	I		
		Amoxicillin/Clavulanic	R		
		Amikacin	R		
		Piperacillin/tazobactam	R		
		Cefotaxime	R		
		Ceftriaxone	R		
		Ceftazidime	R		
		Imipenem	R		
		Meropenem	R		
		Cefepime	R		
		Trimethoprim-sulfamethoxazole	S		
		Levofloxacin	R		
		Cefoxitin	R		
		Doripenem	R		

Aspirate renal abscess

Positive at 10.3 hours.





Empiric antimicrobial choice?

- Administration of effective intravenous antimicrobials ***within the first hour*** of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

- Initial empiric anti-infective therapy of ***one or more drugs*** that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

Crit Care Med 2013; 41:580–637

Combination therapy

- Combination therapy for suspected or known ***Pseudomonas aeruginosa or other multidrug-resistant Gram-negative*** pathogens, pending susceptibility results, increases the likelihood that at least one drug is effective against that strain and positively affects outcome

- Empiric combination therapy ***should not be administered*** for more than 3–5 days.

- De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

Crit Care Med 2007; 35:1888–1895

JAMA 2012; 307:2390–2399

Crit Care Med 2013; 41:580–637

Adequate antimicrobial therapy

- **First,** antimicrobial agent(s) should be initiated as soon as possible after the onset of sepsis

- **Second,** empirically, should be broad enough to cover the potential causative microorganisms

- **Finally,** appropriate antimicrobial dosing to
  - Maximize microbial killing
  - Minimize the development of multidrug antimicrobial resistance and
  - Avoid concentration-related adverse drug reactions.

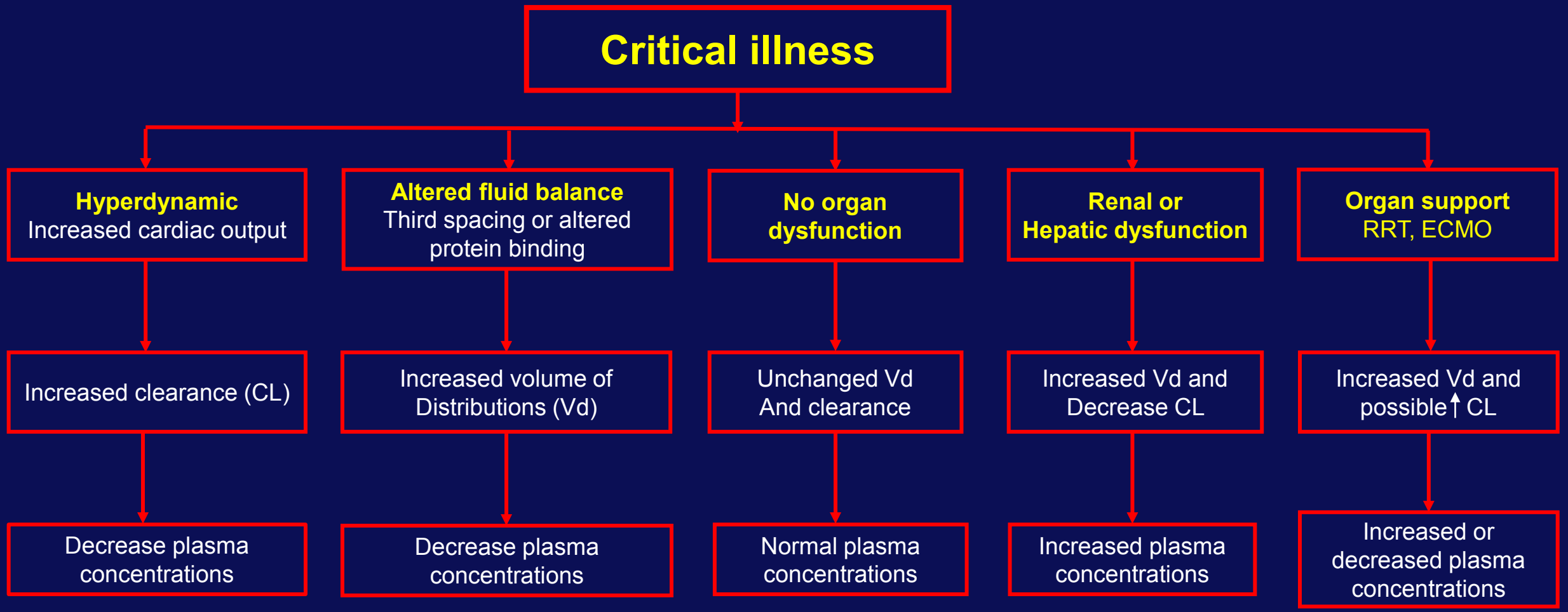
F. Pea. *Clin.Infect.Dis.*2006;42:1764-71

Antibiotic dosing for patients who are critically ill

- Early and appropriated antibiotic administration reduces mortality rates but ***less information is available about the effect of appropriate dose regimens on clinical outcome***

Jason Roberts. Lancet Infect Dis 2014;14:498

The range of altered pathophysiology in patients with critical illness and it effects on drug concentrations



RRT=renal replacement therapy
ECMO=extracorporeal membrane oxygenation

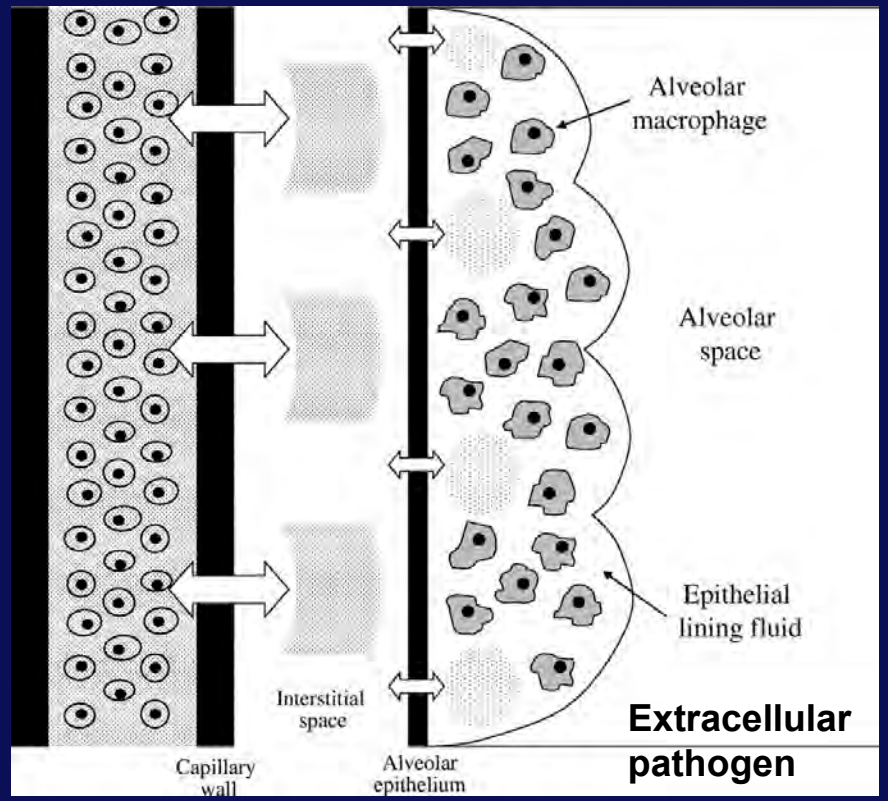
Jason A Roberts. *Lancet Infect Dis* 2014;14:498-509

PK/PD Observed in Critically Ill Patients

- **Volume of distribution change**: Hydrophilic drugs
- **Half life of antibiotics**: Augmented renal clearance
  - (GFR > 130 mL/1.73 m2 in sepsis)
  - Many hydrophilic drugs are eliminate by GFR
- **Hypoalbuminemia**: High protein bound antibiotics
- **Tissue penetration**: Low tissue penetration
- **End Organ dysfunction (Renal) :** Hydrophilic drug
  - Time dependent: Decrease dose
  - Concentration dependent: increase interval
  - Mode of dialysis
- **End Organ dysfunction (Hepatic) :** Lipophilic drug

Advanced Drug Delivery Reviews 2014;77:3–11

Effect of critical illness on antibiotic pharmacokinetics
Pulmonary system



- Optimum antibiotic concentrations in the **Epithelial lining fluid** determine therapeutic success
- The more **lipophilic antibiotics** (Fluroquinolone, macrolides and oxazolidinones) have ***epithelial lining fluid to plasma exposure*** ratio of ***at least 1***
- High exposure ratios are not always seen for hydrophilic antibiotics
- Therefore, hydrophilic drugs → suggest the use of ***higher doses*** in severe pneumonia, ***extended or continuous infusion*** of β lactam antibiotics or administration via nebulization

Jason Roberts. Lancet Infect Dis 2014;14:498

Antibiotics and Sites of infection

Agents	target	antibiotics
Lipid-soluble agents	blood-brain barrier	chloramphenicol, trimethoprim and isoniazid
Highly ionized compound	poor BBB	aminoglycoside
High concentrated in the bile	excreted by liver	ampicillin, doxycycline*
Superior concen in the bone/prostate	bone/prostate	(new) fluroquinolones

* More effective than 1st gen cephalosporins or amimoglycoside (not greatly con in bile) in treating cholangitis

Mandell 2014

Antibiotics and Local factors

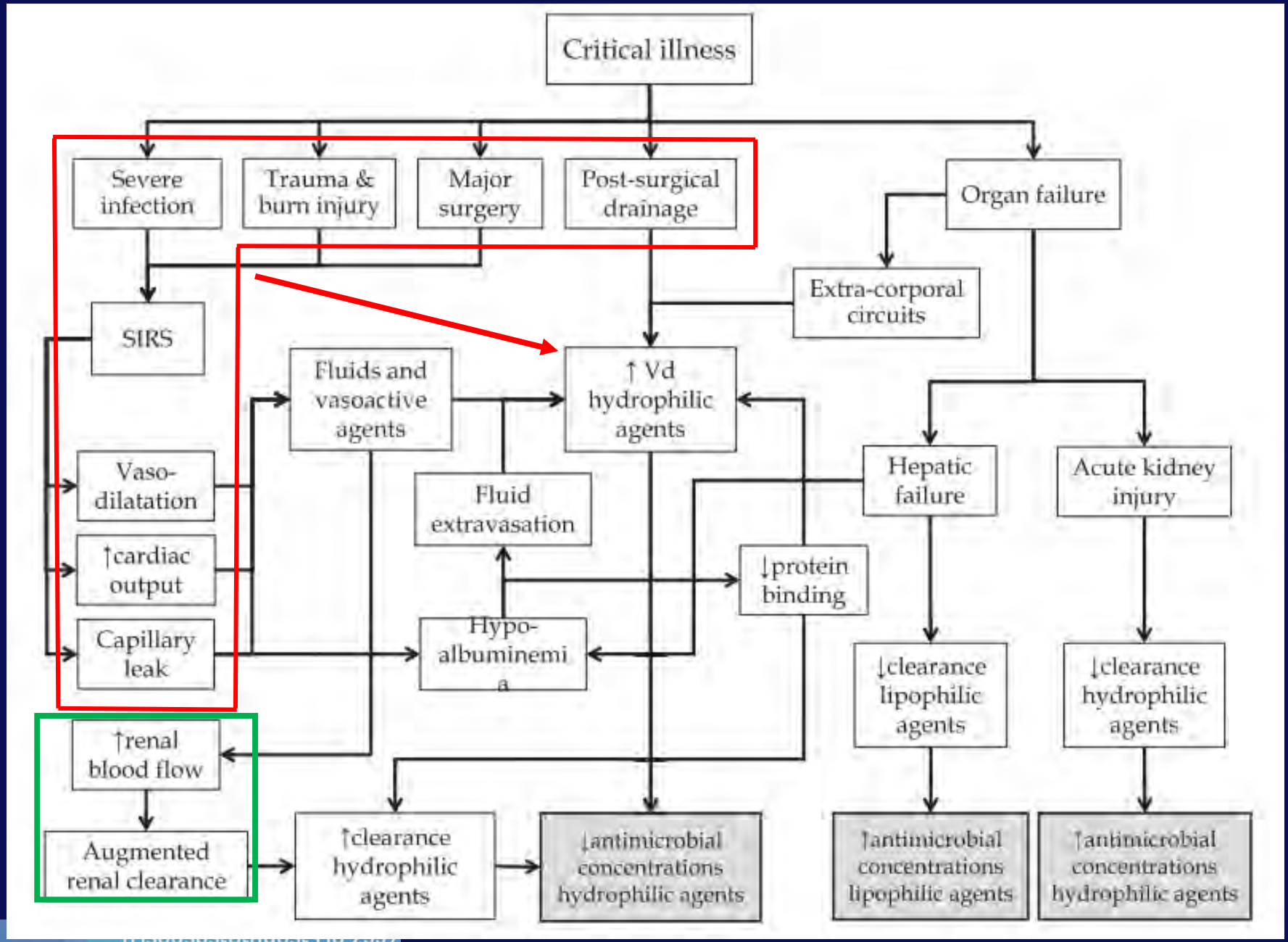
Local factors	sites	poor antibiotics concentration
Pulmonary surfactant	Lung	daptomycin*
Bound to and inactivated by purulent material**	abscesses	Aminiglycoside ***, polymyxins
Bound by hemoglobin	hematoma	penicillin, tetacyclines
Glycocalyx, biofilm	foreign body	interfere with phagocytosis

*daptomycin is bound by pulmonary surfactant

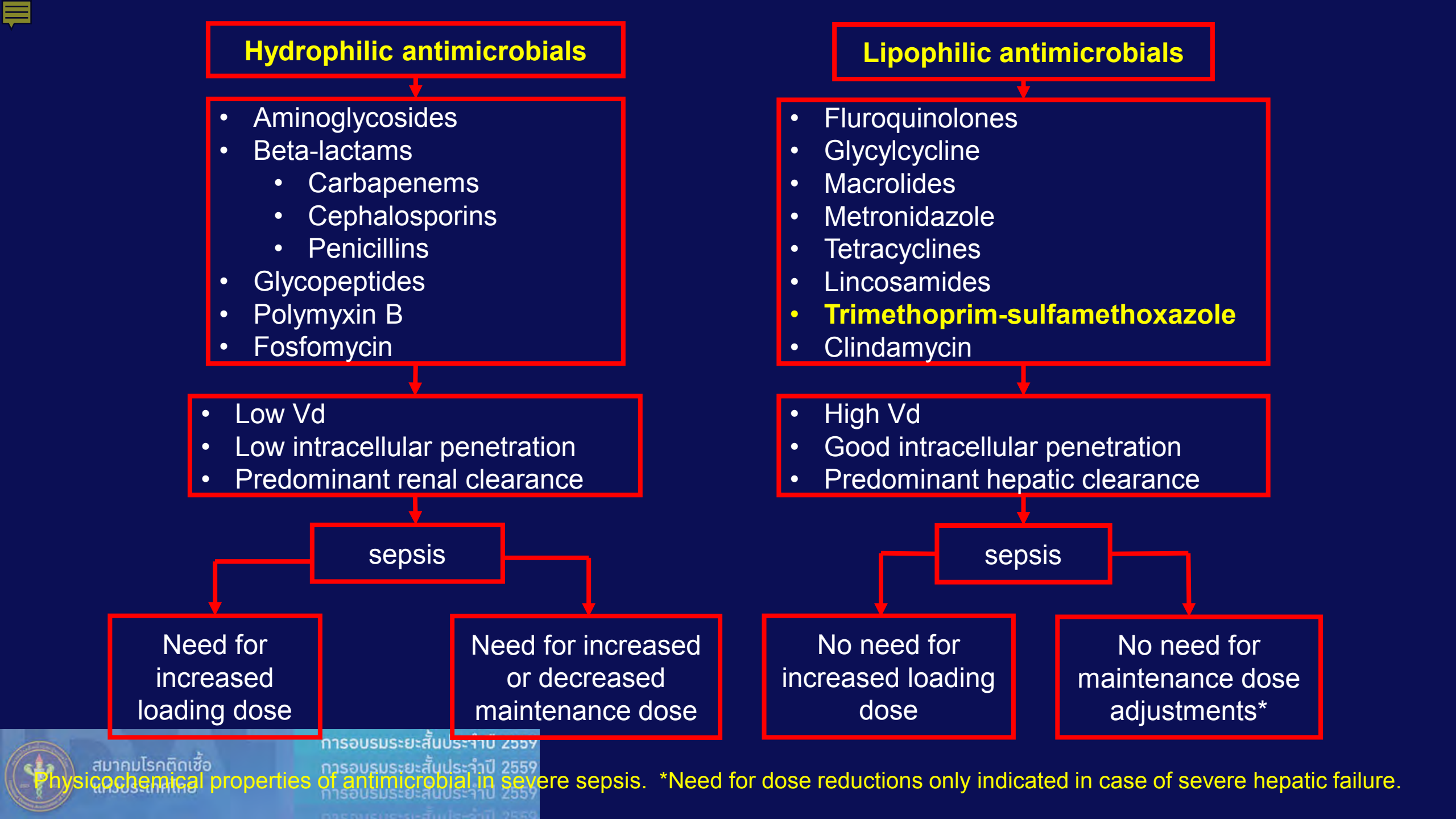
** Penicillin may be more active in purulent material, clinical experience strongly suggests that appropriate drainage greatly enhance the efficacy

*** inactive against anaerobic condition: oxygen is required for the transport of aminoglycoside into the bacterial cell

Mandell 2014



Review of pathophysiological alterations during critical illness and their potential effect on pharmacokinetics of antimicrobial agents. SIRS, systemic inflammatory response syndrome; Vd, volume of distribution.



Physicochemical properties of antimicrobial in severe sepsis. *Need for dose reductions only indicated in case of severe hepatic failure.

Hypoalbuminemia:
High protein bound antibiotics (>85-90%)

- Reduce concentration of albumin could raise the unbound fractions of protein-bound drugs (free drug↑)
- Unbound fractions antibiotic are available not only for **elimination** but also for **distribution**
- Impact on antibiotics that high protein binding

  Ceftriaxone **Ertapenem**
  Cloxacillin **Daptomycin**

- Hypoalbumin may contribute to initial target concentrations but failure to maintain sufficient drug throughout the dosing interval

Jason A Roberts. *Lancet Infect Dis* 2014;14:498-509

Optimal dosage to start antimicrobial therapy

- It must be considered that the target plasma concentration (Ct) that is achieved with the first dose

  - **loading dose (LD)** depends solely on the volume of distribution (Vd) of the drug (LD = Ct × **Vd**)

  - **Maintenance dose (LD)** depends solely on the Clearance of the drug (MD = Ct × **CL**)

Federico Pea1 and Pierluigi Viale, Bench-to-bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock - does the dose matter?, Critical Care 2009, 13:214 (doi:10.1186/cc7774)

Concentration-dependent antibiotics

- The efficacy of these agents is related to the achievement of high ***Cmax/MIC ratio (>10) and AUC/MIC ratio (>100 to 125)***

- Accordingly, ***high dosage***, short-course therapy regimens with a once daily administration schedule may yield more rapid bacterial killing or prevention of resistance development

Federico Pea1 and Pierluigi Viale, Bench-to-bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock - does the dose matter?, Critical Care 2009, 13:214 (doi:10.1186/cc7774)

Time-dependent antibiotics

- strongly suggest that ***extended infusion of β-lactams may improve clinical outcome in critically ill patients*** with severe infections, and indicate that continuous infusion may be the best approach in terms of maximizing efficacy with **time-dependent antimicrobials**.

- Indeed, ***the stability of an antibiotic*** in solution at room temperature is an important consideration when choosing to administer time-dependent antibiotics by continuous infusion

Federico Pea1 and Pierluigi Viale, Bench-to-bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock - does the dose matter?, Critical Care 2009, 13:214 (doi:10.1186/cc7774)

Stability of time-dependent antibiotics in solution for intravenous infusion

Antibiotic	Time of stability at Room temperature (+25°C; hours)	Solvent
Piperacillin/tazobactam	>72	Sterile water for injection
Ceftazidime	24	Sterile water for injection
Imipenem	3.3	Sterile water for injection
Meropenem	5.15	Sterile water for injection
Vancomycin	>696	Sterile water for injection

Stability was defined as times during which antibiotic remains >90% stable in solution

Critical Care 2009, **13:**214

Time dependent antibiotic

Continuous drip vs Conventional

Time dependent antibiotic
Continuous drip vs bolus

Ann Pharm 2006 (Spain) (VAP)	Mero 1 gm drip 360 min q 6 h (N=42)	Mero 1 gm drip 30 min q 6 h (N=47)	P-value
Clinical cure rate	90.47%	59.57%	<0.001
MIC > 0.5	80.95%	29.41%	0.003
MIC 0.25-0.49	100%	76.67%	0.03

Clin Ther 2007 (Spain) (VAP)	Cefta 2 g drip 720 min q 12 h (N=56)	Cefta 2 g drip 30 min q 12 h (N=65)	P-value
Clinical cure rate	89.3%	52.3%	<0.001
MIC = 8	75%	14.3%	0.03
MIC = 4	90%	38.5%	0.02

Time dependent antibiotic
Continuous drip vs bolus

Int J Anti A 2009 (Spain) (VAP)	**Pip/Tazo 4.5 g drip 360 min q 6 h (N=37)**	**Pip/Tazo 4.5 g drip 30 min q 6 h (N=46)**	**P-value**
Clinical cure rate	89.2%	56.5%	<0.001
MIC = 4	90.6%	76%	0.2
MIC = 8	88.9%	40%	0.02
MIC = 16	**87.5%**	**16.7%**	**0.02**

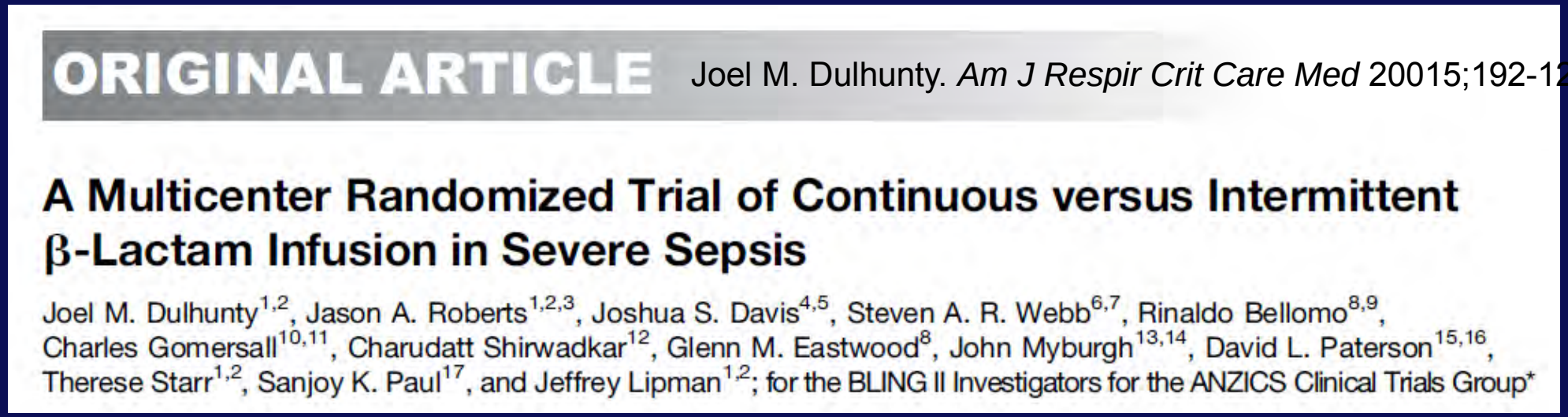
J Crit Care 2010 (USA) (HAP)	**Mero 2 gm drip 3 h q 8 h (N=94)**	**Mero 2 gm drip 30 min q 8 h (N=74)**	**P-value**
Mortality rate	8.5%	21.6%	<0.029

Time dependent antibiotic
Continuous drip vs bolus

CID 2007 (USA) (Pseudomonas sepsis)	Pip/Tazo 3.375 g drip 240 min q 8 h (N=102)	Pip/Tazo 3.375 g drip 30 min q 8 h (N=92)	P-value
Mortality rate			
APACHE II < 17	6.6%	3.7%	0.5
APACHE II ≥ 17	**12.2%**	**31.6%**	**0.04**

Prospective multicenter Double-blind randomized controlled trial

CID 2013 (5 Australia, 1 HK) (Severe sepsis)	Mero or Pip/Tazo continuous infusion (N=30)	Mero or Pip/Tazo bolus (N=30)	P-value
Plasma antibiotic concentration >MIC	82%	29%	0.001
Clinical cure with in 28 days	70%	43%	0.037
Survival hospital discharge	90%	80%	0.47



ORIGINAL ARTICLE

Joel M. Dulhunty. *Am J Respir Crit Care Med* 20015;192-1298-1305

A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

Joel M. Dulhunty[1,2], Jason A. Roberts[1,2,3], Joshua S. Davis[4,5], Steven A. R. Webb[6,7], Rinaldo Bellomo[8,9], Charles Gomersall[10,11], Charudatt Shirwadkar[12], Glenn M. Eastwood[8], John Myburgh[13,14], David L. Paterson[15,16], Therese Starr[1,2], Sanjoy K. Paul[17], and Jeffrey Lipman[1,2]; for the BLING II Investigators for the ANZICS Clinical Trials Group*

- The BLING II study was a prospective, multicenter, double-blind, double-dummy, randomized controlled trial
- It was conducted in 25 ICUs in Australia (17), New Zealand (7), and Hong Kong (1)
- Carbapenem or Piperacillin/Tazobactam
- **The primary outcome was the number of alive ICU-free days at Day 28.**
- Secondary outcomes were 90-day survival, clinical cure 14 days post antibiotic cessation, alive organ failure–free days at Day 14, and duration of bacteremia.

Baseline Characteristics of the Intention-to-Treat Population

	Continuous (*n* = 212)	Intermittent (*n* = 220)
Age, yr	64 (54–72)	65 (53–72)
Sex, male	130 (61.3)	135 (61.4)
APACHE II score	21 (17–26)	20 (16–25)
Immunocompromise	27 (12.7)	34 (15.5)
Study drug		
Piperacillin–tazobactam	147 (69.3)	157 (71.4)
Meropenem	63 (29.7)	60 (27.3)
Ticarcillin–clavulanate	2 (0.9)	3 (1.4)
Site of infection*		
Lung	115 (54.2)	120 (54.5)
Intraabdominal	53 (25.0)	57 (25.9)
Primary bloodstream infection	17 (8.0)	18 (8.2)
Urinary tract	16 (7.5)	18 (8.2)
Skin or skin structure	13 (6.1)	18 (8.2)
Other†	22 (10.4)	12 (5.5)
Unknown	14 (6.6)	14 (6.4)
Organ dysfunction		
Cardiovascular (shock)	154 (72.6)	163 (74.1)
Respiratory	135 (63.7)	139 (63.2)
Metabolic acidosis	68 (32.1)	70 (31.8)
Renal	49 (23.1)	53 (24.1)
Hematologic	26 (12.3)	22 (10.0)

Joel M. Dulhunty. *Am J Respir Crit Care Med* 20015;192-1298-1305

Microbiologic Characteristics

	Continuous (*n* = 40)	Intermittent (*n* = 43)
Gram positive	11 (27.5)	11 (25.6)
Gram negative	29 (72.5)	31 (72.1)
Susceptible to study drug*	39 (97.5)	37 (86.0)
Nonsusceptible to study drug†	1 (2.5)	6 (14.0)

- Identified organisms only 19% of cases
- > 50% were *E.coli* and *Klebsiella pneumoniae, drug resistant less than 4%*

Joel M. Dulhunty. *Am J Respir Crit Care Med* 20015;192-1298-1305

Primary and Secondary Outcomes, Clinical Results, and Adverse Events

	Continuous (*n* = 212)	Intermittent (*n* = 220)	*P* Value
Alive ICU-free days	18 (2–24)	20 (3–24)	0.38
ICU survivors	21 (12–24)	22 (14–25)	0.12
Day-90 survival*†	156 (74.3)	158 (72.5)	0.67
ICU survival†	180 (84.9)	182 (82.7)	0.54
Hospital survival†‡	168 (79.2)	164 (74.9)	0.28
Clinical cure	111 (52.4)	109 (49.5)	0.56
Organ failure–free days	6 (0–10)	6 (0–11)	0.27
Duration of bacteremia, d§	0 (0–0)	0 (0–1)	0.24
ICU length of stay, d‖	7 (3–13)	6 (3–11)	0.042
Hospital length of stay, d‖	16 (8–32)	14 (8–27)	0.25
Adverse events	20 (9.4)	28 (12.7)	0.28
Serious adverse events	19 (9.0)	25 (11.4)	0.41

Joel M. Dulhunty. *Am J Respir Crit Care Med* 20015;192-1298-1305

Discussion
Limitations of the study: Why negative outcome?

1. Microbiological documented only **19% of patients**
   - Possibility that a significant number of patients with noninfectious causes mimicking severe sepsis were enrolled
2. Not demonstrated of MIC
   - **"The theoretical advantage of continuous infusion is crucially dependent on the MIC"** more useful among high MIC
   - Organisms are highly susceptible to antibiotics the probability of not reaching PK-PD target using conventional dosing is very small → very low prevalence of *E.coli* and *K. pneumoniae* resistance (0-4.5%) in Australia
3. Not demonstrated of PK/PD: some beta-lactam need target only 70% fT > MIC to achieve clinical cure, arguing that more prolonged exposure might not be necessary

Studies reporting PK/PD indices from preclinical and clinical assessments, by antibiotic class

Antibiotics	Clinical studies	
Concentration –dependent		
Aminoglycoside	Clinical cure	Cmax/MIC 8-10; AUC/MIC > 70
Time-dependent		
Carbapenems	Clinical cure	75% T>MIC
	Microbiological cure	54% T>MIC
Cephalosporins	Clinical cure	100% T>MIC
	Microbiological cure	60-100% T>MIC
Penicillins	Clinical cure	-
	Microbiological cure	40-50% T>MIC
Concentration –dependent and Time-dependent		
Fluroquinolones	Clinical cure	AUC0-24/MIC >125-250; Cmax/MIC >8
	Microbiological cure	AUC0-24/MIC >34-125; Cmax/MIC >8
Vancomycin	Clinical cure	AUC0-24/MIC >400-450
	Microbiological cure	AUC0-24/MIC >400
Tigecycline	Clinical cure	AUC0-24/MIC >12.8-17.9
	Microbiological cure	AUC0-24/MIC > 6.9-17.9

Jason A Roberts. *Lancet Infect Dis* 2014;14:498-509

General PK characteristics of various antibiotics and possible changes that can occur during fluid shift in critically ill patients

Antibiotic class	Increased Vd with fluid shift	Decreased Cmax with fluid shift	Plasma *T1/2* (h)	Protein binding	CL	TDM required?
Aminoglycosides	Yes	Yes	2-3	Low	by renal function	Yes, to ensure high Cmax and adequate CL
B-lactams	Yes	Yes	0.5-2 (except Ceftri 6-9 h)	Low (except ceftri* & Cloxa	by renal function	optional
Carbapenems	Yes	Yes	1 (except Erta 4 h)	Low (except Ertapenem)	by renal function	optional
Glycopeptides	Yes	Yes	Vanco (4-6)	30-55%	by renal function	to ensure plasma Cmin > 15 mg/mL
Tigecycline	Unlikely	Unlikely	37-66	73-79%	decrease with cholestasis	No
Colistin	likely	likely	2-7.4	Unknown	by renal function	optional

Ceftriaxone > 95% bound to albumin

Hypoalbuminemic in critical ill → unbound drug (free) has a 100 increased CL and 90% greater of Vd

Jason A Roberts. *Crit Care Med* 2009;37(3):843

Antimicrobial Therapy in Patients Receiving Renal Replacement Therapy

- Type of antibiotics
- The mode of RRT
- Mode of replacement fluid administration (predilution or postdilution) and
- **Dose of RRT delivered****
  - **Effluent volume: most important**
  - Effluent volume is dependent on both effluent flow and duration of CRRT
- Filter surface area
- on the ultrafiltration and/or:
  - Very high ultrafiltration flow (QUF) > 2-3 l/hour
- dialysate flow rates (QD)
  - Very high dialysate flow rates (QD) > 1-2 l/hour

F. Pea. Clin Pharmacokinet 2007; 46 (12): 997-1038

J A Jamal Curr Opin Crit Care 2012;18:460-471

Renal replacement therapy vs Antibiotics

- In general drugs with
  - High volumes of distribution (> 1 L/kg)
  - Lipophilic drugs or
  - High protein bound (more than 80%)

poorly eliminated by renal replacement therapy

Renal replacement therapy

- Continuous RRT can be applied as
  - continuous venovenous hemofiltration (CVVH),
  - continuous venovenous hemodialysis (CVVHD), and
  - continuous venovenous hemodiafiltration (CVVHDF)
- Intermittent
- Sustained low-efficiency dialysis (SLED): Hybrid modality

J.A.Jamal. *Curr.Opin.Crit.Care* 2012;18:460-471

Antimicrobial Therapy in Patients Receiving Renal Replacement Therapy

- Removal of solutes from the blood through semi-permeable membranes during RRT may occur by means of two different physicochemical processes, namely, **diffusion or convection**.
  - Intermittent haemodialysis (IHD) is essentially a diffusive technique and
  - CVVH is a convective technique,
  - CVVHDF is a combination of both.
- As a general rule, **the efficiency of drug removal** by the different techniques is expected to be **CVVHDF > CVVH > IHD**
- CLCRRT is expected to be clinically relevant for drugs with dominant renal clearance, especially when presenting **a limited volume of distribution and poor plasma protein binding.**

F. Pea. Clin Pharmacokinet 2007; 46 (12): 997-1038

Antimicrobial Therapy in Patients Receiving Renal Replacement Therapy

- Consistently, CLCRRT should be clinically **relevant particularly for most hydrophilic antimicrobial agents** (e.g. β-lactams, aminoglycosides, glycopeptides), whereas it should assume **much lower relevance for lipophilic compounds** (e.g. fluoroquinolones, oxazolidinones), which generally are nonrenally cleared.

- However, there are ***some notable exceptions***:
  - ceftriaxone and oxacillin, although hydrophilics, are characterised by primary biliary elimination
  - levofloxacin and ciprofloxacin, although lipophilics, are renally cleared.

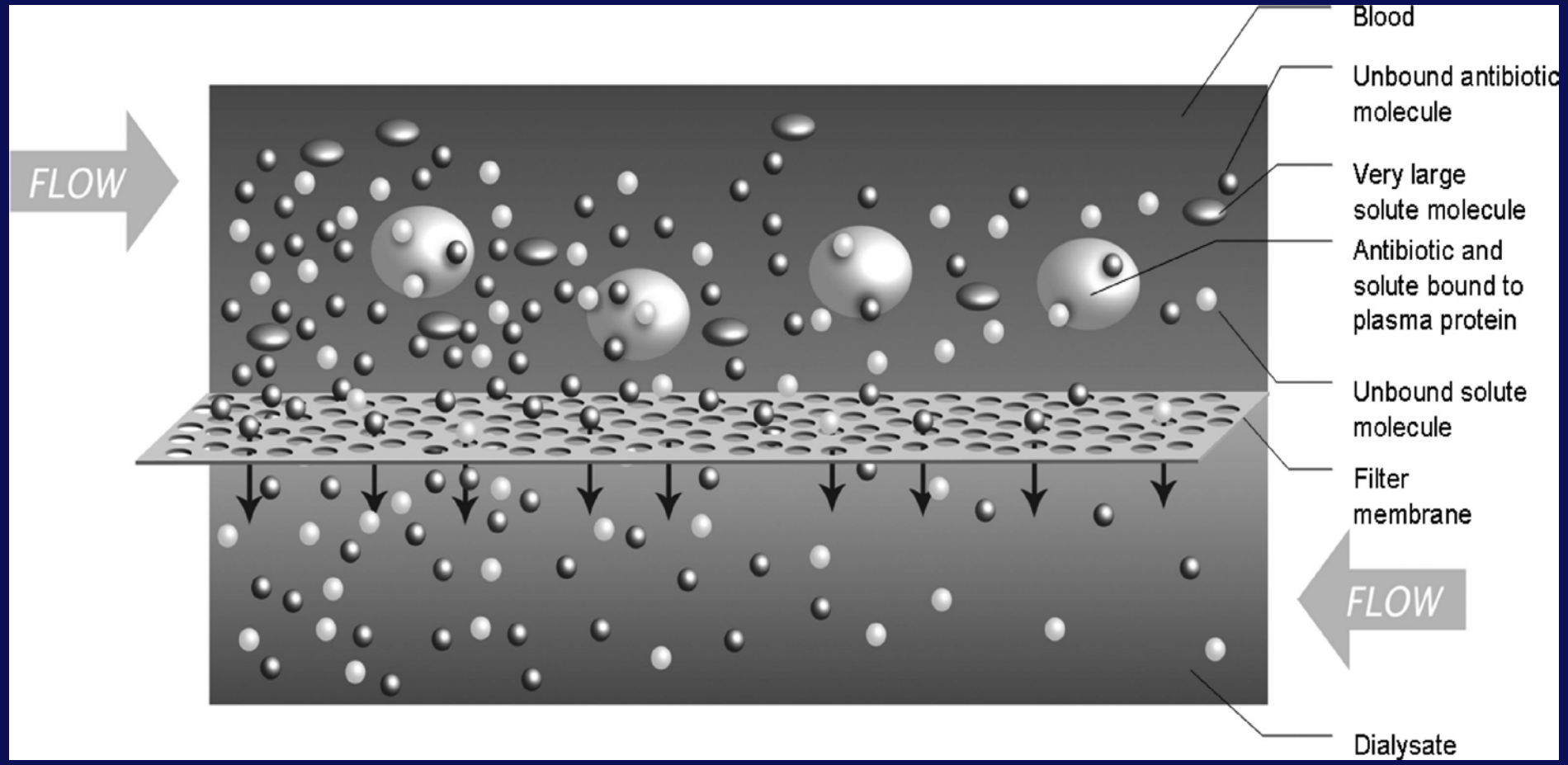
F. Pea. Clin Pharmacokinet 2007; 46 (12): 997-1038

Sustained low-efficiency dialysis (SLED: Hybrid modality)

- All of these approaches are very efficient in removing hydrophilic antimicrobials, in particular those with low protein binding properties and high renal clearance

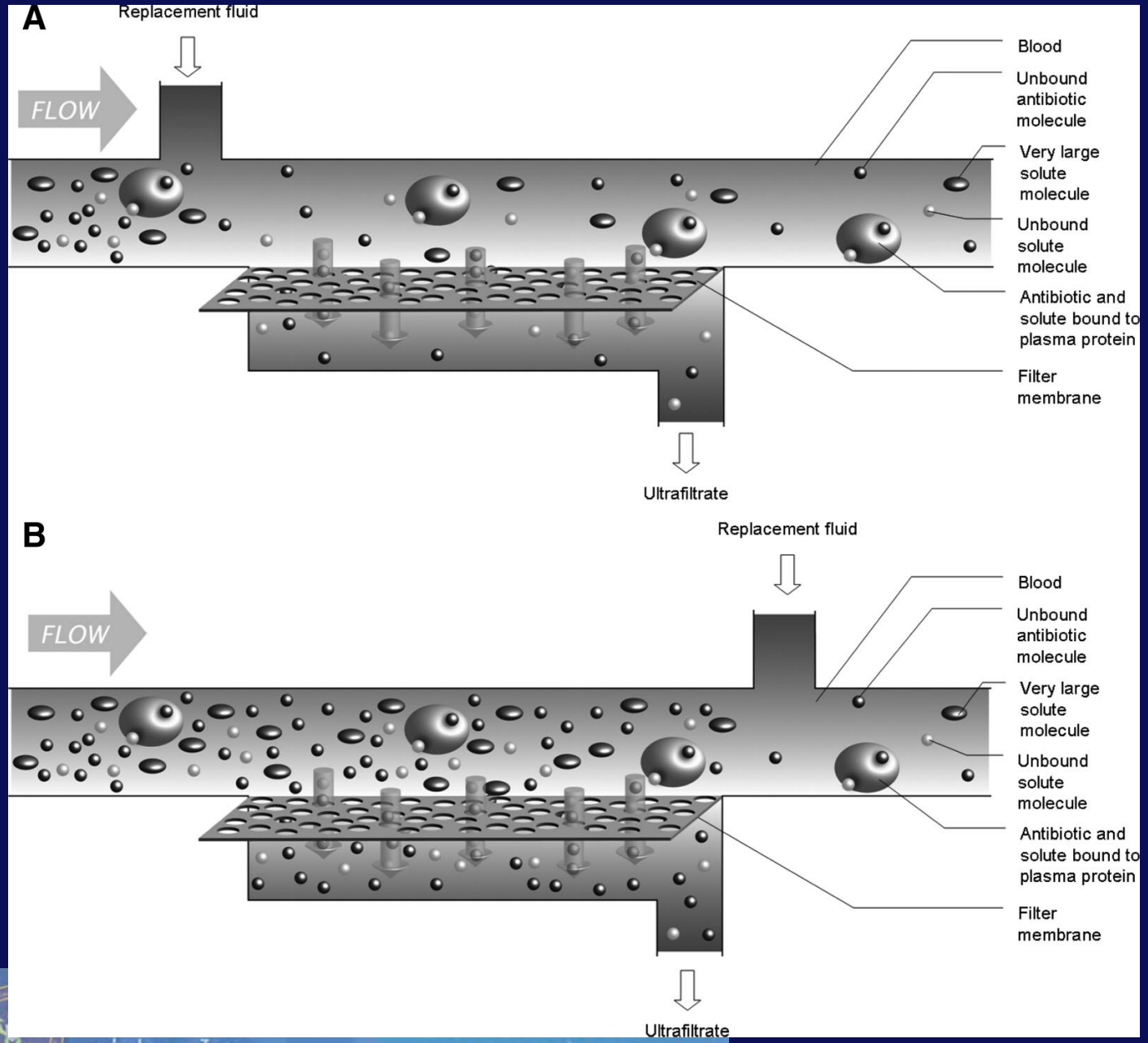
- Time-dependent antibiotics such as β-lactams: need supplemental doses of antibiotics during or follow SLED treatment or prolong infusion times to maintain T>MIC

J A Jamal Curr Opin Crit Care 2012;18:460-471



Continuous venovenous hemodialysis. The countercurrent flow maintains a concentration gradient across the membrane. Protein bound molecules are unable to cross the membrane

G Choi *Crit Care Med* 2009 Vol. 37, No. 7



A, Hemofiltration (continuous venovenous hemofiltration) (predilution). Dilution of blood with replacement fluid before the blood enters the filter results in a fall in concentration in the filter and hence a reduction in efficiency of solute removal. Protein bound molecules are unable to cross the membrane.

B, Hemofiltration (continuous venovenous hemofiltration) (postdilution).

G Choi *Crit Care Med* 2009 Vol. 37, No. 7

Critical ill septic patient

Loading dose: Vd→ hydrophilic drugs
Maintain dose: CL

Large volume of distribution

- Large volume resuscitate
- Invasive ventilation
- Surgical procedure

Initial High Loading Dose

Renal or hepatic impairment

No

- Vasopressors
- Increase CO
- Increase diuresis

Increase Clearance or Augmented Renal Clearance (ARC) (>120 ml/min per 1.73 m2)

Maintain high dose

Reassess after 48-72 hr.

Any of:

- Bacteria with low MIC
- Normalization of creatinine clearance
- Sepsis resolution

Yes

Adjust dose accordingly

Adjust Dose

Conclusions

- We should start antimicrobial within 1 hours after diagnosis
- Initial empiric anti-infective therapy of ***one or more drugs*** that have activity against all likely pathogens
- Combination empirical therapy for
  - Neutropenic patients with severe sepsis
  - Multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp., CRE
    - BL/BI plus aminoglycide or quinolone or
    - Carbapenem plus aminoglycide or quinolone
- Empiric combination therapy ***should not be administered*** for more than 3–5 days.
- Source control is also very important

Conclusions

- **Five main issues can be detected in critically ill patients regarding altered PK:**
  - increased volume of distribution (Vd),
  - altered protein binding,
  - augmented renal clearance,
  - impaired renal clearance and
  - hepatic dysfunction

Conclusions

- **loading dose (LD)** depends on the volume of distribution (Vd) of the drug
- **Maintenance dose (LD)** depends on the Clearance of the drug
- **Volume of distribution change in critical illness**: Hydrophilic drugs → suboptimal level
- **Time dependent antibiotics**: prefer CI or extended infusion (Stability and drug compatibility), particularly in high MIC organisms.

Thank you for your attentions!